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(54) Title: CELLULAR ACCUMULATION OF PHOSPHONATE ANALOGS OF HIV PROTEASE INHIBITOR COMPOUNDS

(57) Abstract: Phosphonate substituted compounds with HIV protease inhibitory properties having use as therapeutics and for other industrial purposes are disclosed. The compositions inhibit 5 HIV protease activity and/or are useful therapeutically for the treatment of AIDS and other antiviral infections, as well as in assays for the detection of HIV protease.



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**CELLULAR ACCUMULATION OF PHOSPHONATE ANALOGS OF
HIV PROTEASE INHIBITOR COMPOUNDS**

10 This non-provisional application claims the benefit of Provisional Applications
60/375,622, filed April 26, 2002; Provisional Application No. 60/375,779 filed April 26,
2002; Provisional Application No. 60/375,834, filed April 26, 2002, and Provisional
Application No. 60/375,665 filed April 26, 2002, all of which are incorporated herein by
reference. Additionally, copending applications Attorney Docket Nos. 259.PC and 260.PC
15 filed concurrently with this application are also incorporated herein by reference in their
entirety.

FIELD OF THE INVENTION

The invention relates generally to compounds with antiviral activity and more
specifically with anti-HIV protease properties.

20

BACKGROUND OF THE INVENTION

AIDS is a major public health problem worldwide. Although drugs targeting HIV
viruses are in wide use and have shown effectiveness, toxicity and development of resistant
strains have limited their usefulness. Assay methods capable of determining the presence,
absence or amounts of HIV viruses are of practical utility in the search for inhibitors as well
25 as for diagnosing the presence of HIV.

Human immunodeficiency virus (HIV) infection and related disease is a major public health problem worldwide. The retrovirus human immunodeficiency virus type 1 (HIV-1), a member of the primate lentivirus family (DeClercq E (1994) *Annals of the New York Academy of Sciences*, 724:438-456; Barre-Sinoussi F (1996) *Lancet*, 348:31-35), is generally
5 accepted to be the causative agent of acquired immunodeficiency syndrome (AIDS) Tarrago et al *FASEB Journal* 1994, 8:497-503). AIDS is the result of repeated replication of HIV-1 and a decrease in immune capacity, most prominently a fall in the number of CD4+ lymphocytes. The mature virus has a single stranded RNA genome that encodes 15 proteins (Frankel et al (1998) *Annual Review of Biochemistry*, 67:1-25; Katz et al (1994) *Annual*
10 *Review of Biochemistry*, 63:133-173), including three key enzymes: (i) protease (Prt) (von der Helm K (1996) *Biological Chemistry*, 377:765-774); (ii) reverse transcriptase (RT) (Hottiger et al (1996) *Biological Chemistry Hoppe-Seyler*, 377:97-120), an enzyme unique to retroviruses; and (iii) integrase (Asante et al (1999) *Advances in Virus Research* 52:351-369; Wlodawer A (1999) *Advances in Virus Research* 52:335-350; Esposito et al (1999) *Advances*
15 *in Virus Research* 52:319-333). Protease is responsible for processing the viral precursor polyproteins, integrase is responsible for the integration of the double stranded DNA form of the viral genome into host DNA and RT is the key enzyme in the replication of the viral genome. In viral replication, RT acts as both an RNA- and a DNA-dependent DNA polymerase, to convert the single stranded RNA genome into double stranded DNA. Since
20 virally encoded Reverse Transcriptase (RT) mediates specific reactions during the natural reproduction of the virus, inhibition of HIV RT is an important therapeutic target for treatment of HIV infection and related disease.

Sequence analysis of the complete genomes from several infective and non-infective HIV-isolates has shed considerable light on the make-up of the virus and the types of
25 molecules that are essential for its replication and maturation to an infective species. The HIV protease is essential for the processing of the viral gag and gag-pol polypeptides into mature virion proteins. L. Ratner, et al., *Nature*, 313:277-284 (1985); L. H. Pearl and W. R. Taylor, *Nature*, 329:351 (1987). HIV exhibits the same gag/pol/env organization seen in other retroviruses. L. Ratner, et al., above; S. Wain-Hobson, et al., *Cell*, 40:9-17 (1985); R.
30 Sanchez-Pescador, et al., *Science*, 227:484-492 (1985); and M. A. Muesing, et al., *Nature*, 313:450-458 (1985).

A therapeutic target in AIDS involves inhibition of the viral protease (or proteinase)

that is essential for processing HIV-fusion polypeptide precursors. In HIV and several other retroviruses, the proteolytic maturation of the gag and gag/pol fusion polypeptides (a process indispensable for generation of infective viral particles) has been shown to be mediated by a protease that is, itself, encoded by the pol region of the viral genome. Y. Yoshinaka, et al.,
 5 Proc. Natl. Acad. Sci. USA, 82:1618-1622 (1985); Y. Yoshinaka, et al., J. Virol., 55:870-873 (1985); Y. Yoshinaka, et al., J. Virol., 57:826-832 (1986); and K. von der Helm, Proc. Natl. Acad. Sci., USA, 74:911-915 (1977). Inhibition of the protease has been shown to inhibit the processing of the HIV p55 in mammalian cell and HIV replication in T lymphocytes. T. J. McQuade, et al., Science, 247:454 (1990).

10 Drugs approved in the United States for AIDS therapy include nucleoside inhibitors of RT (Smith et al (1994) *Clinical Investigator*, 17:226-243), protease inhibitors and non-nucleoside RT inhibitors (NNRTI), (Johnson et al (2000) *Advances in Internal Medicine*, 45 (1-40; Porche DJ (1999) *Nursing Clinics of North America*, 34:95-112).

The protease (or proteinase), consisting of only 99 amino acids, is among the smallest
 15 enzymes known, and its demonstrated homology to aspartyl proteases such as pepsin and renin (L. H. Pearl and W. R. Taylor, Nature, 329:351-354 (1987); and I. Katoh, et al., Nature, 329:654-656 (1987)), led to inferences regarding the three-dimensional structure and mechanism of the enzyme (L. H. Pearl and W. R. Taylor, above) that have since been borne out experimentally. Active HIV protease has been expressed in bacteria (see, e.g., P. L.

20 Darke, et al., J. Biol. Chem., 264:2307-2312 (1989)) and chemically synthesized (J. Schneider and S. B. Kent, Cell, 54:363-368 (1988); and R. F. Nutt, et al., Proc. Natl. Acad. Sci., USA, 85:7129-7133 (1988)). Site directed mutagenesis (P. L. Darke, et al., above); and N. E. Kohl, et al., Proc. Natl. Acad. Sci., USA, 85:4686-4690 (1988)) and pepstatin inhibition (P. L. Darke, et al., J. Biol. Chem., 264:2307-2312 (1989); S. Seelmeier, et al., Proc. Natl.

25 Acad. Sci., USA, 85:6612-6616 (1988); C.-Z. Giam and I. Borsos, J. Biol. Chem., 263:14617-14720 (1988); and J. Hansen, et al., EMBO J., 7:1785-1791 (1988)) have provided evidence for HIV protease's mechanistic function as an aspartyl protease. A study has demonstrated that the protease cleaves at the sites expected in peptides modeled after the regions actually cleaved by the enzyme in the gag and pol precursor proteins during viral
 30 maturation. P. L. Darke, et al., Biochem. Biophys. Res. Commun., 156:297-303 (1988). X-ray crystallographic analysis of the HIV-protease (M. A. Navia, et al., Nature, 337:615-620 (1989)) and a related retroviral enzyme from Rous sarcoma virus (M. Miller, et al., Nature,

337:576-579 (1989)) reveal an active site in the protease dimer that is identical to that seen in other aspartyl proteases, thus supporting the supposition (L. H. Pearl and W. R. Taylor, above) that the HIV enzyme is active as a dimer. See also Joseph A. Martin, "Recent Advances in the Design of HIV Proteinase Inhibitors," *Antiviral Research*, 17 (1992) 265-278.

Inhibitors of HIV protease are useful to limit the establishment and progression of infection by therapeutic administration as well as in diagnostic assays for HIV. Protease inhibitor drugs approved by the FDA include:

- saquinavir (Invirase®, Fortovase®, Hoffman-La Roche, EP-00432695 and EP-00432694)
- ritonavir (Norvir®, Abbott Laboratories)
- indinavir (Crixivan®, Merck & Co.)
- nelfinavir (Viracept®, Pfizer)
- amprenavir (Agenerase®, GlaxoSmithKline, Vertex Pharmaceuticals)
- lopinavir/ritonavir (Kaletra®, Abbott Laboratories)

Experimental protease inhibitor drugs include:

- fosamprenavir (GlaxoSmithKline, Vertex Pharmaceuticals)
- tipranavir (Boehringer Ingelheim)
- atazanavir (Bristol-Myers Squibb).

There is a need for anti-HIV therapeutic agents, i.e. drugs having improved antiviral and pharmacokinetic properties with enhanced activity against development of HIV resistance, improved oral bioavailability, greater potency and extended effective half-life *in vivo*. New HIV protease inhibitors (PI) should be active against mutant HIV strains, have distinct resistance profiles, fewer side effects, less complicated dosing schedules, and orally active. In particular, there is a need for a less onerous dosage regimen, such as one pill, once per day. Although drugs targeting HIV protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains have limited their usefulness (Palella, et al *N. Engl. J. Med.* (1998) 338:853-860; Richman, D. D. *Nature* (2001) 410:995-1001).

Combination therapy of PI and RT inhibitors has proven to be highly effective in suppressing viral replication to unquantifiable levels for a sustained period of time. Also,

combination therapy with RT and protease inhibitors have shown synergistic effects in suppressing HIV replication. Unfortunately, many patients currently fail combination therapy due to the development of drug resistance, non-compliance with complicated dosing regimens, pharmacokinetic interactions, toxicity, and lack of potency. Therefore, there is a
5 need for new HIV protease inhibitors that are synergistic in combination with other HIV inhibitors.

Improving the delivery of drugs and other agents to target cells and tissues has been the focus of considerable research for many years. Though many attempts have been made to develop effective methods for importing biologically active molecules into cells, both *in vivo*
10 and *in vitro*, none has proved to be entirely satisfactory. Optimizing the association of the inhibitory drug with its intracellular target, while minimizing intercellular redistribution of the drug, e.g. to neighboring cells, is often difficult or inefficient.

Most agents currently administered to a patient parenterally are not targeted, resulting in systemic delivery of the agent to cells and tissues of the body where it is unnecessary, and
15 often undesirable. This may result in adverse drug side effects, and often limits the dose of a drug (e.g., cytotoxic agents and other anti-cancer or anti-viral drugs) that can be administered. By comparison, although oral administration of drugs is generally recognized as a convenient and economical method of administration, oral administration can result in either (a) uptake of the drug through the cellular and tissue barriers, e.g. blood/brain,
20 epithelial, cell membrane, resulting in undesirable systemic distribution, or (b) temporary residence of the drug within the gastrointestinal tract. Accordingly, a major goal has been to develop methods for specifically targeting agents to cells and tissues. Benefits of such treatment includes avoiding the general physiological effects of inappropriate delivery of such agents to other cells and tissues, such as uninfected cells. Intracellular targeting may be
25 achieved by methods and compositions which allow accumulation or retention of biologically active agents inside cells.

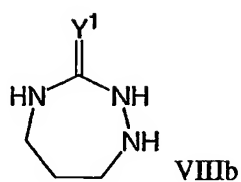
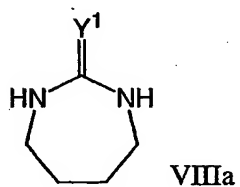
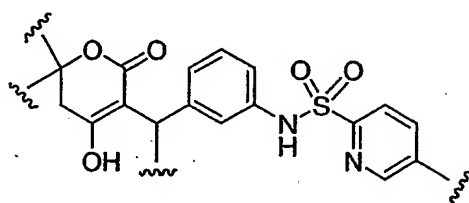
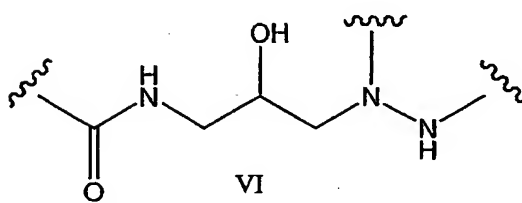
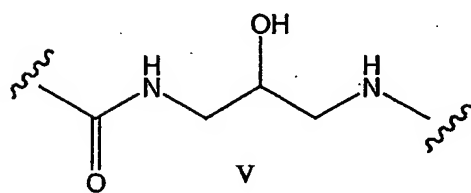
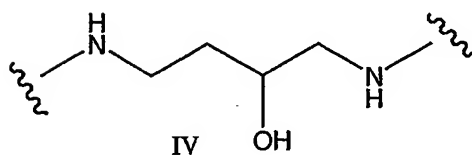
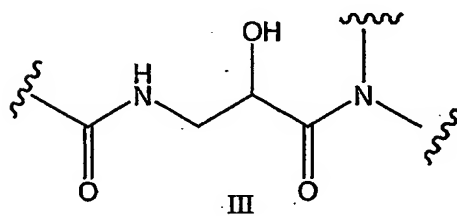
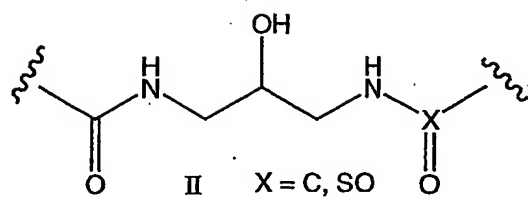
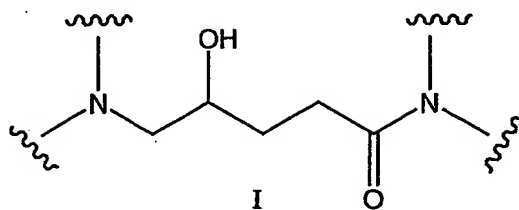
SUMMARY OF THE INVENTION

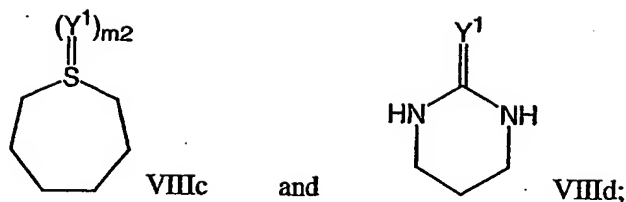
The present invention provides novel compounds with HIV protease activity, i.e. novel human retroviral protease inhibitors. Therefore, the compounds of the invention may inhibit retroviral proteases and thus inhibit the replication of the virus. They are useful for treating human patients infected with a human retrovirus, such as human immunodeficiency virus (strains of HIV-1 or HIV-2) or human T-cell leukemia viruses (HTLV-I or HTLV-II) which results in acquired immunodeficiency syndrome (AIDS) and/or related diseases. The present invention includes novel phosphonate HIV protease inhibitor (PI) compounds and phosphonate analogs of known approved and experimental protease inhibitors. The compounds of the invention optionally provide cellular accumulation as set forth below.

The present invention relates generally to the accumulation or retention of therapeutic compounds inside cells. The invention is more particularly related to attaining high concentrations of phosphonate-containing molecules in HIV infected cells. Intracellular targeting may be achieved by methods and compositions which allow accumulation or retention of biologically active agents inside cells. Such effective targeting may be applicable to a variety of therapeutic formulations and procedures.

Compositions of the invention include new PI compounds having at least one phosphonate group. The invention includes all known approved and experimental protease inhibitors with at least one phosphonate group.

In one aspect, the invention includes compounds having Formulas I, II, III, IV, V, VI, VII and VIIIa-d:





where a wavy line indicates the other structural moieties of the compounds.

Formulas I- VIII are substituted with one or more covalently attached groups, including at least one phosphonate group. Formulas I-VIII are "scaffolds", i.e. substructures which are common to the specific compounds encompassed therein.

Another aspect of the invention provides a pharmaceutical combination comprising an effective amount of a compound selected from Formulas I-VIII and a second compound having anti-HIV properties.

Another aspect of the invention provides a method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises administering to, i.e. treating, said animal with a pharmaceutical combination comprising an effective amount of a compound selected from Formulas I-VIII and a second compound having anti-HIV properties.

The invention provides a pharmaceutical composition comprising an effective amount of a compound selected from Formulas I-VIII, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

This invention pertains to a method of increasing cellular accumulation and retention of drug compounds, thus improving their therapeutic and diagnostic value.

The invention also provides a method of inhibiting HIV, comprising administering to a mammal infected with HIV (HIV positive) an amount of a compound of Formulas I-VIII, effective to inhibit the growth of said HIV infected cells.

The invention also provides a compound selected from Formulas I-VIII for use in medical therapy (preferably for use in treating cancer, e.g. solid tumors), as well as the use of a compound of Formulas I-VIII for the manufacture of a medicament useful for the treatment of cancer, e.g. solid tumors.

The invention also provides processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Some of the compounds of Formulas I-

VIII are useful to prepare other compounds of Formulas I-VIII.

In another aspect of the invention, the activity of HIV protease is inhibited by a method comprising the step of treating a sample suspected of containing HIV virus with a compound or composition of the invention.

5 Another aspect of the invention provides a method for inhibiting the activity of HIV protease comprising the step of contacting a sample suspected of containing HIV virus with a composition of the invention.

In other aspects, novel methods for synthesis analysis, separation, isolation, purification, characterization, and testing of the compounds of this invention are provided.

10

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying description, structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it
15 will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein are intended
20 to have the following meanings:

The terms "phosphonate" and "phosphonate group" mean a functional group or moiety within a molecule that comprises at least one phosphorus-carbon bond, and at least one phosphorus-oxygen double bond. The phosphorus atom is further substituted with oxygen, sulfur, and nitrogen substituents. These substituents may be part of a prodrug
25 moiety. As defined herein, "phosphonate" and "phosphonate group" include molecules with phosphonic acid, phosphonic monoester, phosphonic diester, phosphoramidate, phosphondiamidate and phosphonthioate functional groups.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e. active ingredient, as a result of
30 spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or

metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically-active compound.

“Pharmaceutically acceptable prodrug” refers to a compound that is metabolized in the host, for example hydrolyzed or oxidized, by either enzymatic action or by general acid or base solvolysis, to form an active ingredient. Typical examples of prodrugs of the compounds of the invention have biologically labile protecting groups on a functional moiety of the compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, esterified, deesterified, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated, photolyzed, hydrolyzed, or other functional group change or conversion involving forming or breaking chemical bonds on the prodrug.

“Prodrug moiety” means a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, “Design and Application of Prodrugs” in Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-\text{CH}_2\text{OC}(=\text{O})\text{R}^9$ and acyloxymethyl carbonates $-\text{CH}_2\text{OC}(=\text{O})\text{OR}^9$ where R^9 is C_1 – C_6 alkyl, C_1 – C_6 substituted alkyl, C_6 – C_{20} aryl or C_6 – C_{20} substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. In certain compounds of the invention, a prodrug moiety is part of a phosphonate group. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-\text{CH}_2\text{OC}(=\text{O})\text{OC}(\text{CH}_3)_3$.

The phosphonate group may be a phosphonate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphoramidate-ester group.

5 Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (DeLambert et al (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho*-or *para*-position may
10 accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, e.g. esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C-O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al (1992) *J. Chem. Soc. Perkin Trans. I* 2345; Brook et al WO 91/19721. Still
15 other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier et al WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the
20 disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion et al, US Patent No. 6312662).

"Protecting group" refers to a moiety of a compound that masks or alters the
25 properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as intermediates in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York,
30 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound

alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

5 Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon
10 conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro*, in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g. alcohols, be
15 physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

Any reference to any of the compounds of the invention also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali
20 metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1 – C_4 alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids;
25 and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound of an hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_1 – C_4 alkyl group).

For therapeutic use, salts of active ingredients of the compounds of the invention will
30 be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable

compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

"Alkyl" is C₁-C₁₈ hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (n-Pr, n-propyl, -CH₂CH₂CH₃), 2-propyl (*i*-Pr, *i*-propyl, -CH(CH₃)₂), 1-butyl (n-Bu, n-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (*i*-Bu, *i*-butyl, -CH₂CH(CH₃)₂), 2-butyl (s-Bu, s-butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (*t*-Bu, *t*-butyl, -C(CH₃)₃), 1-pentyl (n-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃).

"Alkenyl" is C₂-C₁₈ hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, *sp*² double bond. Examples include, but are not limited to: ethylene or vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), cyclopentenyl (-C₅H₇), and 5-hexenyl (-CH₂CH₂CH₂CH₂CH=CH₂).

"Alkynyl" is C₂-C₁₈ hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, *sp* triple bond. Examples include, but are not limited to: acetylenic (-C≡CH) and propargyl (-CH₂C≡CH),

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to: methylene (-CH₂-), 1,2-ethyl (-CH₂CH₂-), 1,3-propyl (-CH₂CH₂CH₂-), 1,4-butyl (-CH₂CH₂CH₂CH₂-), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to: 1,2-ethylene (-CH=CH-).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but are not limited to: acetylene ($-\text{C}\equiv\text{C}-$), propargyl ($-\text{CH}_2\text{C}\equiv\text{C}-$),
 5 and 4-pentynyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}-$).

"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

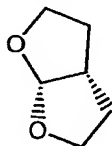
10 "Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to
 15 20 carbon atoms, e.g. the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms.

"Substituted alkyl", "substituted aryl", and "substituted arylalkyl" mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a substituent. Typical substituents include, but are not limited to, $-\text{X}$, $-\text{R}$, $-\text{O}-$,
 20 $-\text{OR}$, $-\text{SR}$, $-\text{S}^-$, $-\text{NR}_2$, $-\text{NR}_3$, $=\text{NR}$, $-\text{CX}_3$, $-\text{CN}$, $-\text{OCN}$, $-\text{SCN}$, $-\text{N}=\text{C}=\text{O}$, $-\text{NCS}$, $-\text{NO}$, $-\text{NO}_2$, $=\text{N}_2$, $-\text{N}_3$, $\text{NC}(=\text{O})\text{R}$, $-\text{C}(=\text{O})\text{R}$, $-\text{C}(=\text{O})\text{NRR}$, $-\text{S}(=\text{O})_2\text{O}^-$, $-\text{S}(=\text{O})_2\text{OH}$, $-\text{S}(=\text{O})_2\text{R}$, $-\text{OS}(=\text{O})_2\text{OR}$, $-\text{S}(=\text{O})_2\text{NR}$, $-\text{S}(=\text{O})\text{R}$, $-\text{OP}(=\text{O})\text{O}_2\text{RR}$, $-\text{P}(=\text{O})\text{O}_2\text{RR}$, $-\text{P}(=\text{O})(\text{O})_2$, $-\text{P}(=\text{O})(\text{OH})_2$, $-\text{C}(=\text{O})\text{R}$, $-\text{C}(=\text{O})\text{X}$, $-\text{C}(\text{S})\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{O}^-$, $-\text{C}(\text{S})\text{OR}$, $-\text{C}(\text{O})\text{SR}$, $-\text{C}(\text{S})\text{SR}$, $-\text{C}(\text{O})\text{NRR}$, $-\text{C}(\text{S})\text{NRR}$, $-\text{C}(\text{NR})\text{NRR}$, where each X is independently a halogen: F, Cl, Br, or I; and each
 25 R is independently $-\text{H}$, alkyl, aryl, heterocycle, protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

"Heterocycle" as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry
 30 of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566.

Examples of heterocycles include by way of example and not limitation pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinoliny, isoquinoliny, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, bis-tetrahydrofuranyl, tetrahydropyranyl, bis-tetrahydropyranyl, tetrahydroquinoliny, tetrahydroisoquinoliny, decahydroquinoliny, octahydroisoquinoliny, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indoliziny, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinoliziny, phthalazinyl, naphthyridinyl, quinoxaliny, quinazoliny, cinnoliny, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazoliny, pyrazolidinyl, pyrazoliny, piperazinyl, indoliny, isoindoliny, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazoliny, and isatinoyl.

One embodiment of the bis-tetrahydrofuranyl group is:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at

position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β -carboline. Still
5 more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetetyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Carbocycle" means a saturated, unsaturated or aromatic ring having 3 to 7 carbon atoms as a monocycle or 7 to 12 carbon atoms as a bicycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring
10 atoms, e.g. arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

15 "Linker" or "link" means a chemical moiety comprising a covalent bond or a chain of atoms that covalently attaches a phosphonate group to a drug. Linkers include portions of substituents A¹ and A³ enumerated in Formula I, or substituents A₁ and A₃ enumerated in Formula II, which include moieties such as: repeating units of alkyloxy (e.g. polyethylenoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino, Jeffamine™); and diacid
20 ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical
25 constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as
30 electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l, D and L, or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

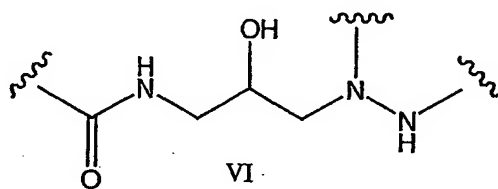
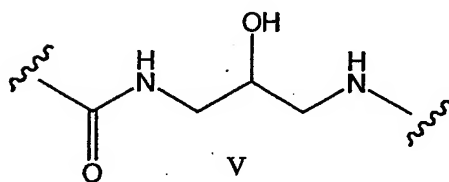
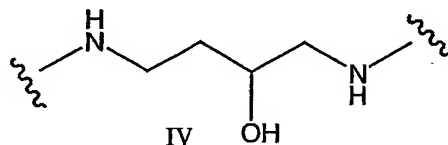
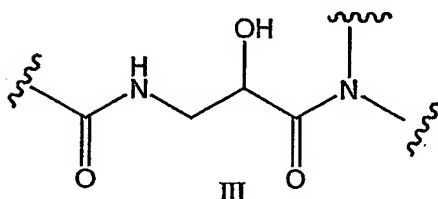
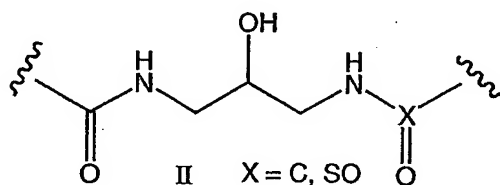
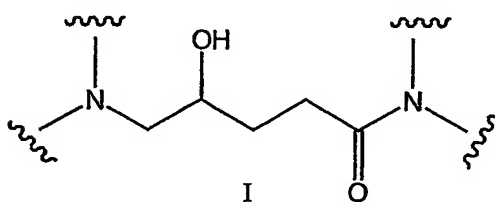
HIV Protease Inhibitor Compounds

The compounds of the invention include those with HIV protease inhibitory activity. In particular, the compounds include HIV protease inhibitors. The compounds of the inventions bear a phosphonate group, which may be a prodrug moiety.

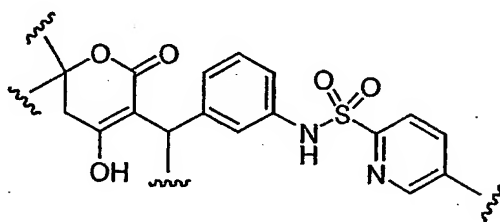
In various embodiments of the invention one identifies compounds that may fall within the generic scope of the documents cited under the definition of the terms ILPPI (Indinavir-like phosphonate protease inhibitors, Formula I); AMLPPI (Amprenavir-like phosphonate protease inhibitors, Formula II); KNILPPI (KNI-like phosphonate protease inhibitors, Formula III); RLPPI (Ritonavir-like phosphonate protease inhibitors, Formula IV); LLPPI (Lopinavir-like phosphonate protease inhibitors, Formula IV); NLPPI (Nelfinavir-like phosphonate protease inhibitors, Formula V); SLPPI (Saquinavir-like phosphonate protease inhibitors, Formula V); ATLPPI (Atanzavir-like phosphonate protease inhibitors, Formula VI); TLPPI (Tipranavir-like phosphonate protease inhibitors, Formula VII); and CCLPPI (Cyclic carbonyl-like phosphonate protease inhibitors, Formula VIIIa-d) all of which comprise a phosphonate group, e.g. a phosphonate diester, phosphoramidate-ester prodrug, or a phosphondiamidate-ester (Jiang et al, US 2002/0173490 A1).

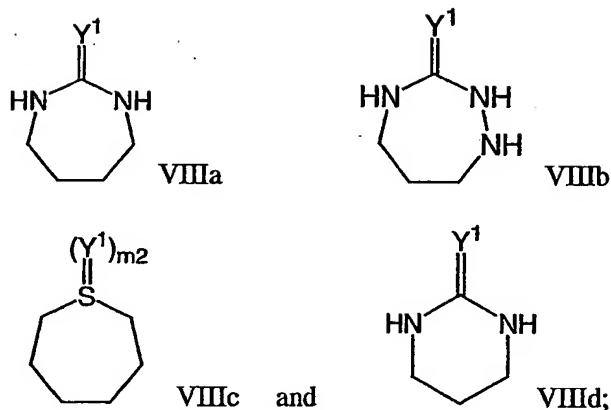
Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R¹" or "R^{6a}", then it will be understood that the groups may be the same or different, i.e., each group is independently selected. Wavy lines indicate the site of covalent bond attachments to the adjoining groups, moieties, or atoms.

- 5 Compounds of the invention are set forth in the schemes, examples, descriptions and claims below and include the invention includes compounds having Formulas I, II, III, IV, V, VI, VII and VIIIa-d:



10



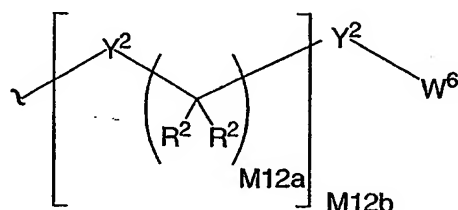


5 where a wavy line indicates the other structural moieties of the compounds.

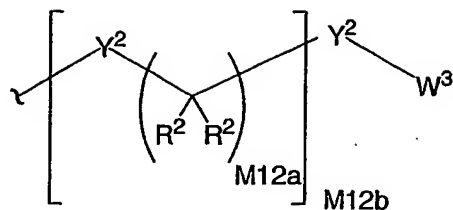
Formula I compounds have a 3-hydroxy-5-amino-pentamide core. Formula II compounds have a 2-hydroxy-1, 3-amino-propylamide or 2-hydroxy-1,3-amino-propylaminosulfone core. Formula III compounds have a 2-hydroxy-3-amino-propylamide core. Formula IV compounds have a 2-hydroxy-4-amino-butylamine core. Formula V compounds have a acylated 1,3-diaminopropane core. Formula VI compounds have a 2-hydroxy-3-diaza-propylamide core. Formula VII compounds have a sulfonamide 5,6-dihydro-4-hydroxy-2-pyrone core. Formula VIIIa-d compounds have a six or seven-membered ring, and a cyclic carbonyl, sulfhydryl, sulfoxide or sulfone core, where Y¹ is oxygen, sulfur, or substituted nitrogen and m₂ is 0, 1 or 2.

15 Formulas I, II, III, IV, V, VI, VII and VIIIa-d are substituted with one or more covalently attached groups, including at least one phosphonate group. Formulas I, II, III, IV, V, VI, VII and VIIIa-d are substituted with one or more covalently attached A⁰ groups, including simultaneous substitutions at any or all A⁰. A⁰ is A¹, A² or W³. Compounds of Formulas I, II, III, IV, V, VI, VII and VIIIa-d include at least one A¹.

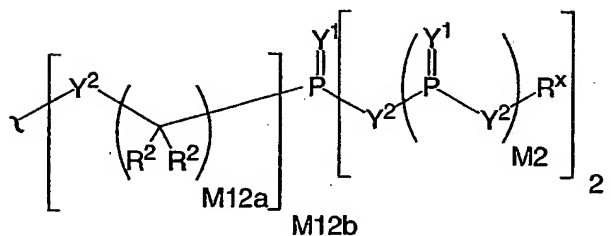
20 A¹ is:



A² is:



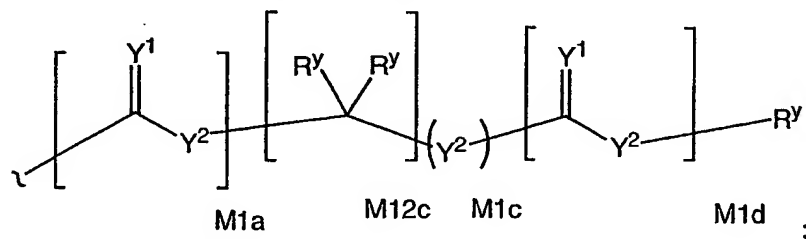
A³ is:



Y¹ is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or N(N(R^x)(R^x)).

5 Y² is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), N(N(R^x)(R^x)),
-S(O)_{M2}-, or -S(O)_{M2}-S(O)_{M2}-.

R^x is independently H, W³, a protecting group, or the formula:



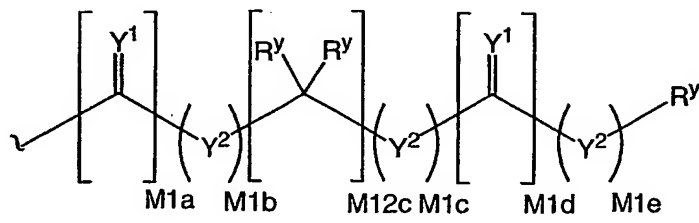
wherein:

10 M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12; and

R^y is independently H, W³, R² or a protecting group.

Alternatively, R^x is a group of the formula:



15

wherein:

m1a, m1b, m1c, m1d and m1e are independently 0 or 1;

m12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

R^y is H, W³, R² or a protecting group;

provided that:

if m1a, m12c, and m1d are 0, then m1b, m1c and m1e are 0;

5 if m1a and m12c are 0 and m1d is not 0, then m1b and m1c are 0;

if m1a and m1d are 0 and m12c is not 0, then m1b and at least one of m1c and m1e are 0;

if m1a is 0 and m12c and m1d are not 0, then m1b is 0;

if m12c and m1d are 0 and m1a is not 0, then at least two of m1b, m1c and m1e are 0;

10 if m12c is 0 and m1a and m1d are not 0, then at least one of m1b and m1c are 0; and

if m1d is 0 and m1a and m12c are not 0, then at least one of m1c and m1e are 0.

R¹ is independently H or alkyl of 1 to 18 carbon atoms.

R² is independently H, R³ or R⁴ wherein each R⁴ is independently substituted with 0 to 3 R³ groups. Alternatively, taken together at a carbon atom, two R² groups form a ring, i.e. a spiro carbon. The ring may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The ring may be substituted with 0 to 3 R³ groups.

R³ is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R³ is bound to a heteroatom, then R³ is R^{3c} or R^{3d}.

R^{3a} is F, Cl, Br, I, -CN, N₃ or -NO₂.

20 R^{3b} is Y¹.

R^{3c} is -R^x, -N(R^x)(R^x), -SR^x, -S(O)R^x, -S(O)₂R^x, -S(O)(OR^x), -S(O)₂(OR^x), -OC(Y¹)R^x, -OC(Y¹)OR^x, -OC(Y¹)(N(R^x)(R^x)), -SC(Y¹)R^x, -SC(Y¹)OR^x, -SC(Y¹)(N(R^x)(R^x)), -N(R^x)C(Y¹)R^x, -N(R^x)C(Y¹)OR^x, or -N(R^x)C(Y¹)(N(R^x)(R^x)).

R^{3d} is -C(Y¹)R^x, -C(Y¹)OR^x or -C(Y¹)(N(R^x)(R^x)).

25 R⁴ is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms.

R⁵ is R⁴ wherein each R⁴ is substituted with 0 to 3 R³ groups.

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R³ groups.

30 W³ is W⁴ or W⁵.

W⁴ is R⁵, -C(Y¹)R⁵, -C(Y¹)W⁵, -SO₂R⁵, or -SO₂W⁵.

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups.

W^{3a} is W^{4a} or W^{5a} .

W^{4a} is R^{5a} , $-C(Y^1)R^{5a}$, $-C(Y^1)W^{5a}$, $-SO_2R^{5a}$, or $-SO_2W^{5a}$.

5 W^{5a} is a multivalent substituted carbocycle or heterocycle wherein W^{5a} is independently substituted with 0 to 3 R^2 groups.

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups.

M2 is 0, 1 or 2;

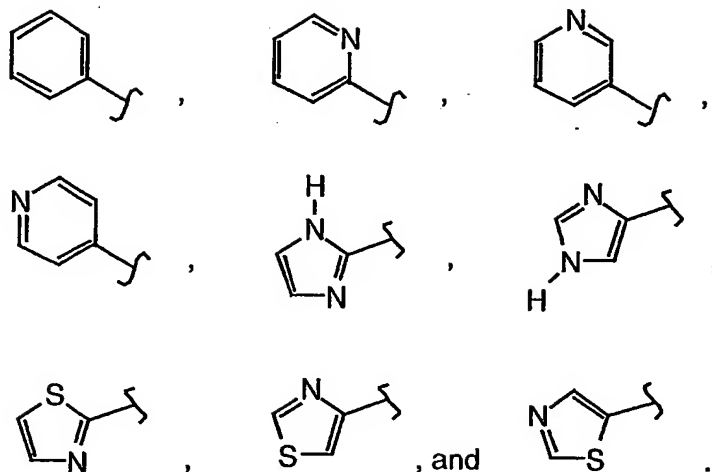
M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12; and

10 M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

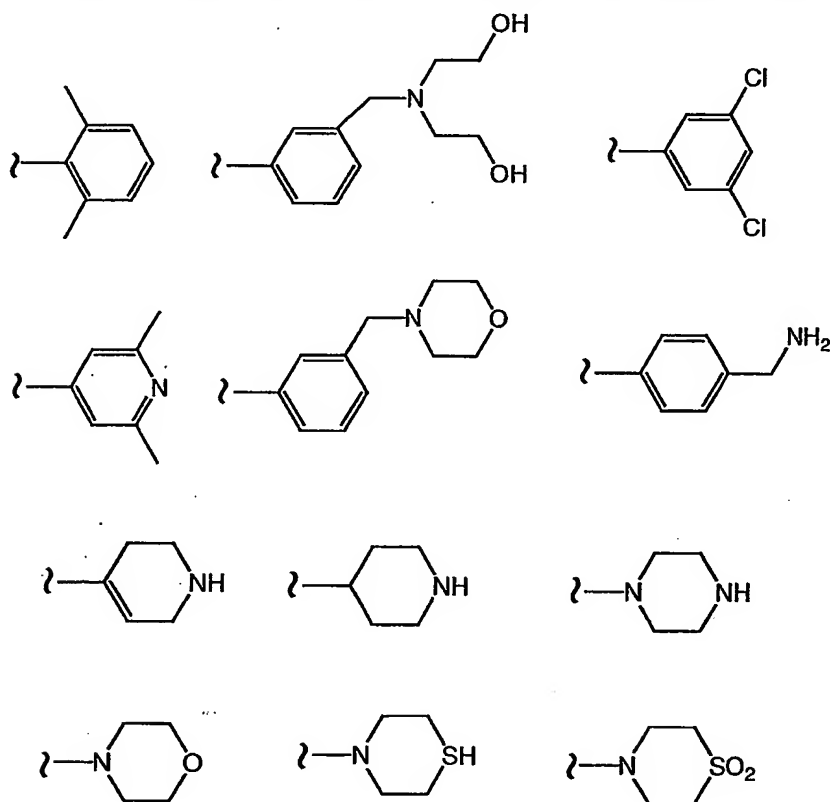
W^5 and W^{5a} carbocycles and W^5 and W^{5a} heterocycles may be independently substituted with 0 to 3 R^2 groups. W^5 may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. W^5 may have 3 to 10 ring atoms, e.g., 3 to 7 ring atoms. The W^5 rings are saturated when containing 3 ring atoms, saturated or
15 mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

A W^5 or W^{5a} heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to
20 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W^5 and W^{5a} heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). W^5 and W^{5a} heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a
25 bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W^5 heterocycle may be bonded to Y^2 through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

W^5 and W^{5a} heterocycles include for example, pyridyl, dihydropyridyl isomers,
30 piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. W^5 also includes, but is not limited to, examples such as:

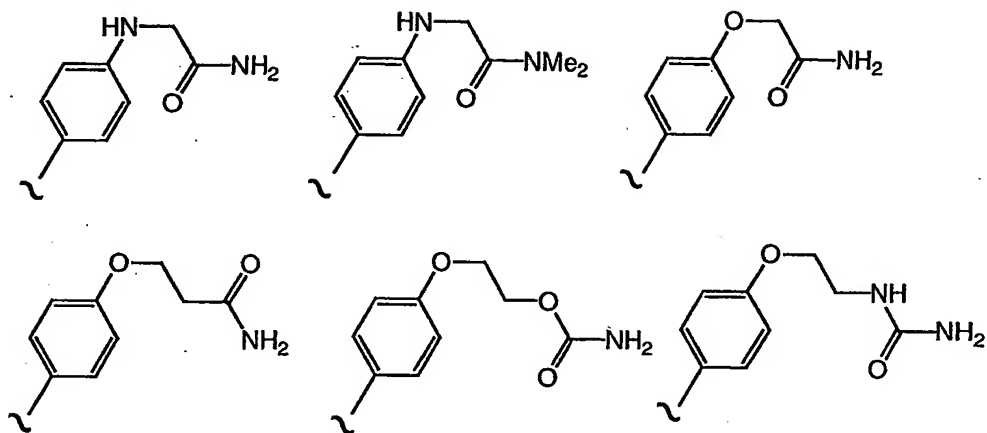


W^5 and W^{5a} carbocycles and heterocycles may be independently substituted with 0 to 3 R^2 groups, as defined above. For example, substituted W^5 carbocycles include:

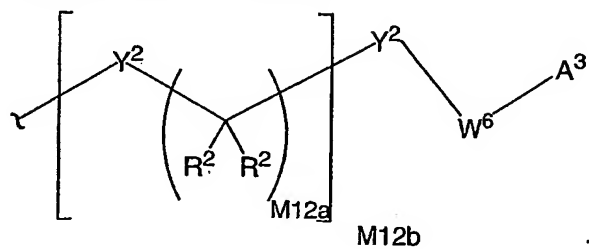


5

Examples of substituted phenyl carbocycles include:

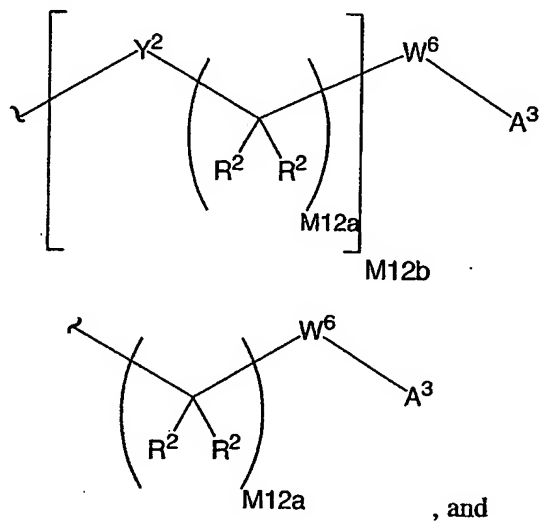


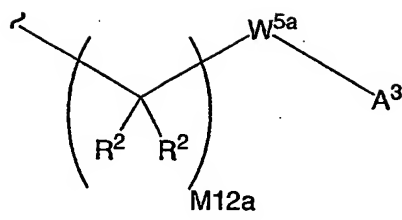
Embodiments of A¹ include:



5

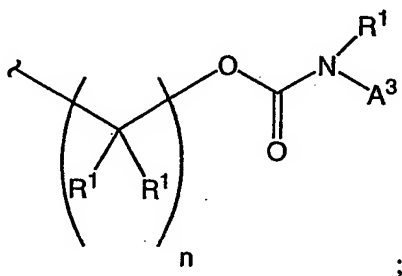
and where one or more Y² are a bond, such as:





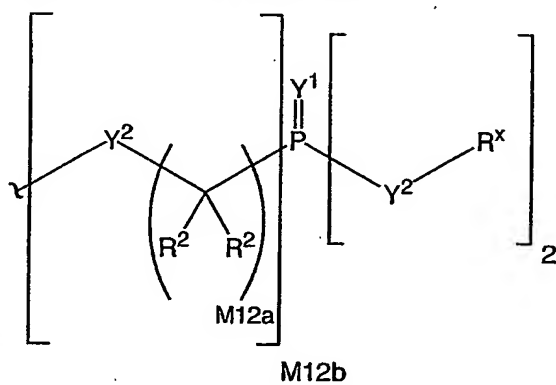
where W^{5a} is a carbocycle or a heterocycle and W^{5a} is independently substituted with 0 or 1 R^2 groups.

5 Embodiments of A^1 also include:



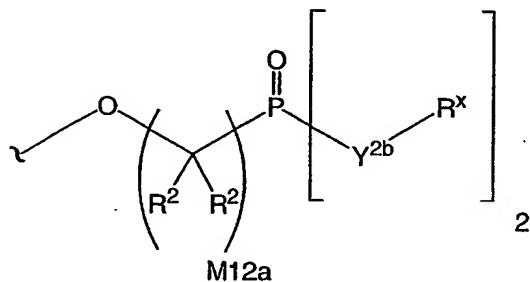
where n is an integer from 1 to 18.

Embodiments of A^3 include where $M2$ is 0, such as:

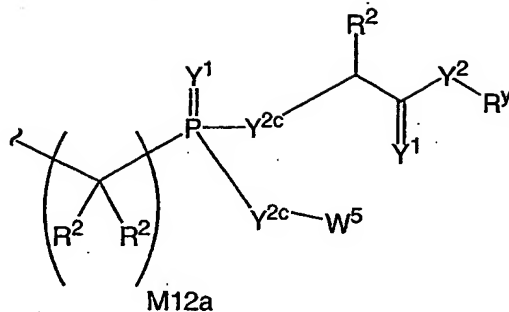


10

and where $M12b$ is 1, Y^1 is oxygen, and Y^{2b} is oxygen (O) or nitrogen ($N(R^x)$) such as:

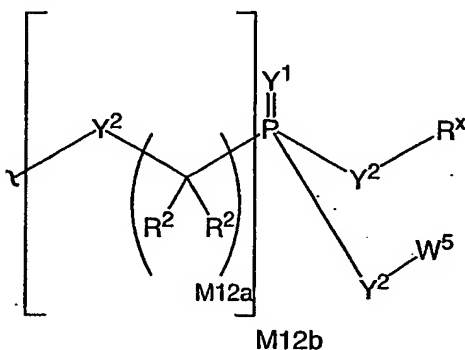


An embodiment of A³ includes:

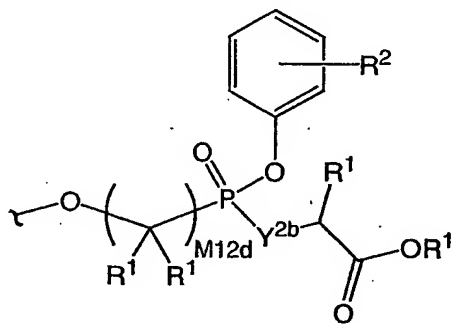


where Y^{2c} is O, N(R^y) or S. For example, R¹ may be H and n may be 1.

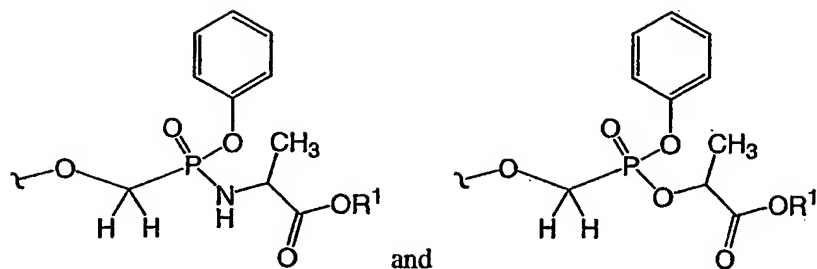
Another embodiment of A³ includes:



where W⁵ is a carbocycle such as phenyl or substituted phenyl. Such embodiments include:

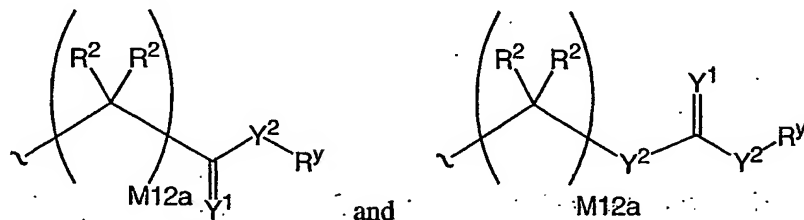


where Y^{2b} is O or N(R^x); M12d is 1, 2, 3, 4, 5, 6, 7 or 8; and the phenyl carbocycle is substituted with 0 to 3 R² groups. Such embodiments of A³ include phenyl phosphoramidate amino acid, e.g. alanate esters and phenyl phosphonate-lactate esters:

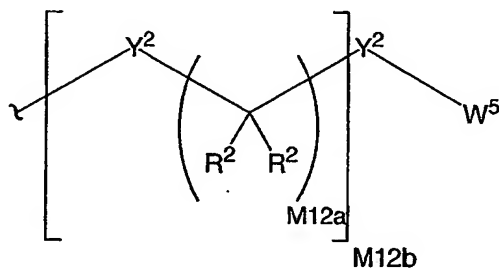


The chiral carbon of the amino acid and lactate moieties may be either the R or S configuration or the racemic mixture.

- 5 Embodiments of R^x include esters, carbamates, carbonates, thioesters, amides, thioamides, and urea groups:



Embodiments of A^2 include where W^3 is W^5 , such as:

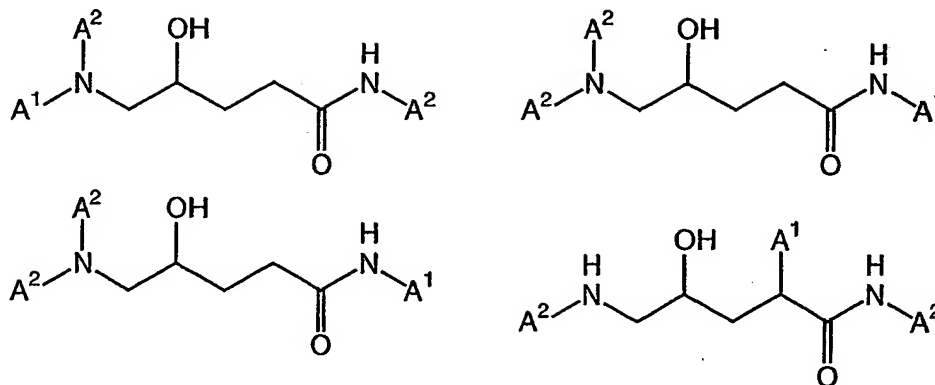


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Alternatively, A^2 is phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl or substituted pyridyl.

Exemplary embodiments of Formula I compounds include, but are not limited to, structures:

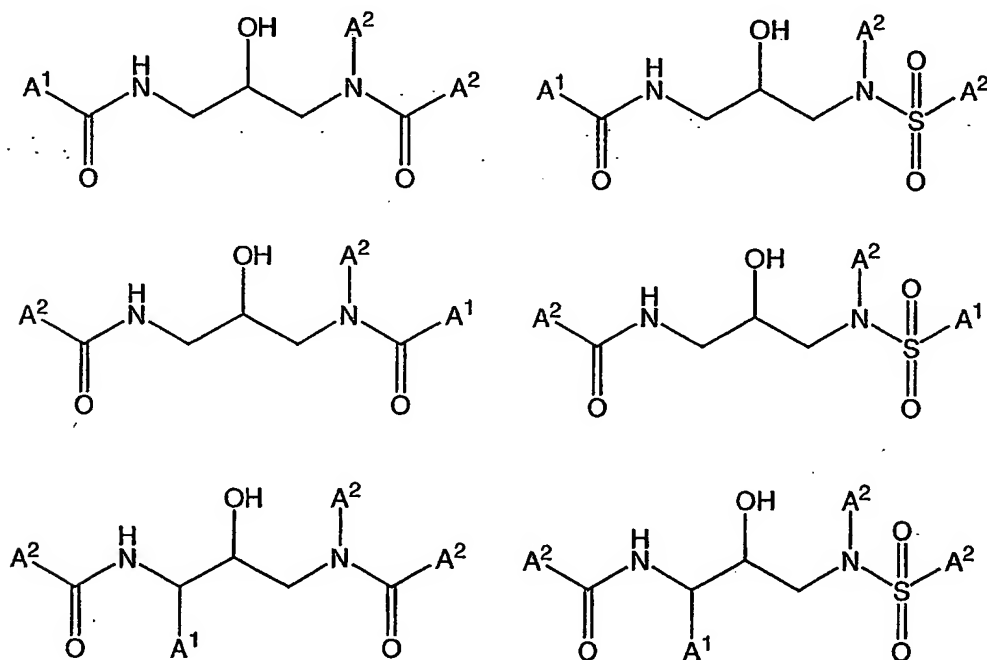
15



where A¹ denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula II compounds include, but are not limited to, structures:

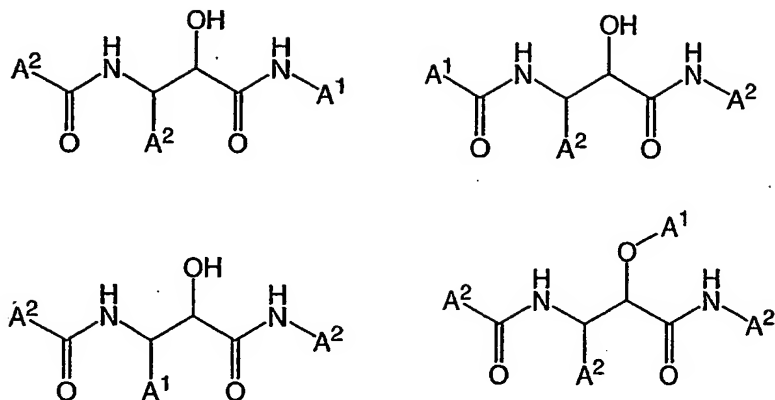
5



where A¹ denotes a covalent attachment site of a phosphonate group.

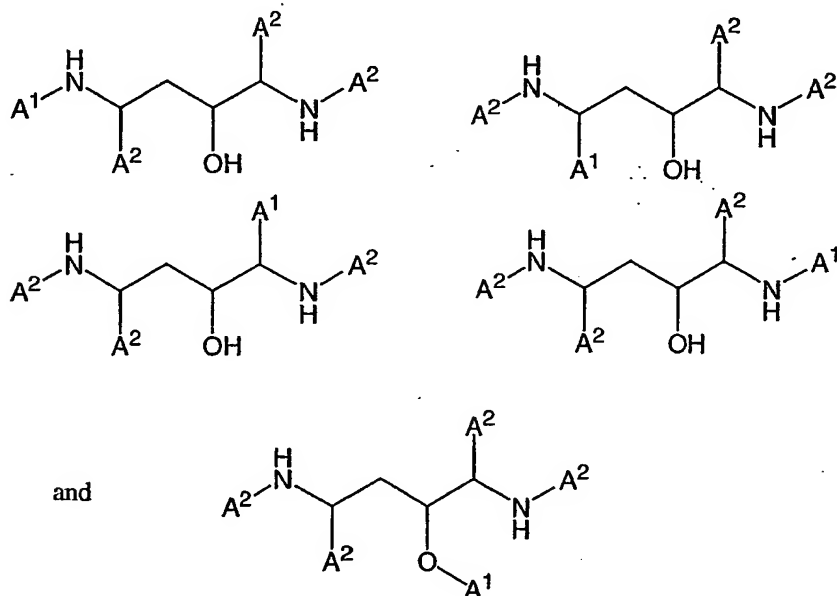
Exemplary embodiments of Formula III compounds include, but are not limited to, structures:

10



where A^1 denotes a covalent attachment site of a phosphonate group.

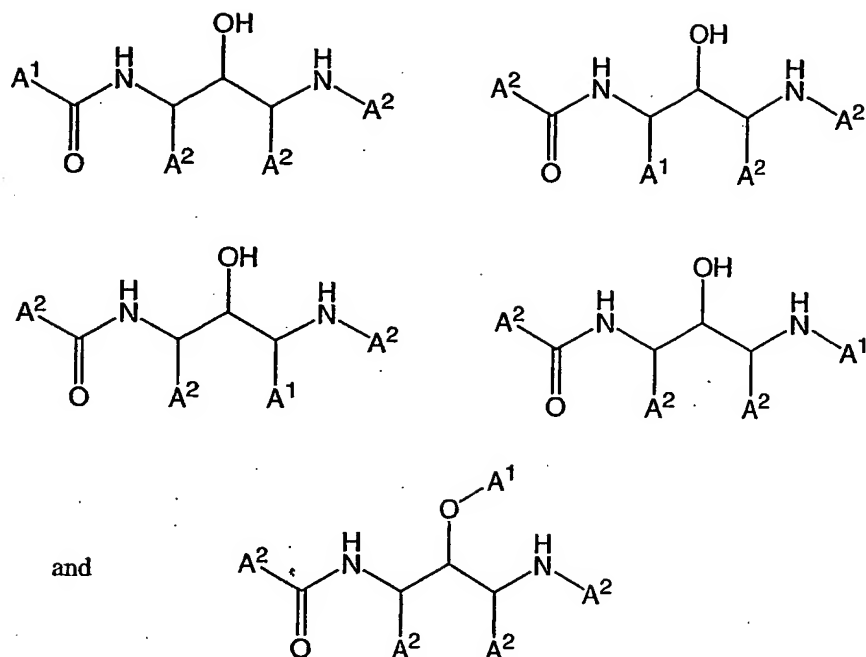
Exemplary embodiments of Formula IV compounds include, but are not limited to, structures:



5

where A^1 denotes a covalent attachment site of a phosphonate group.

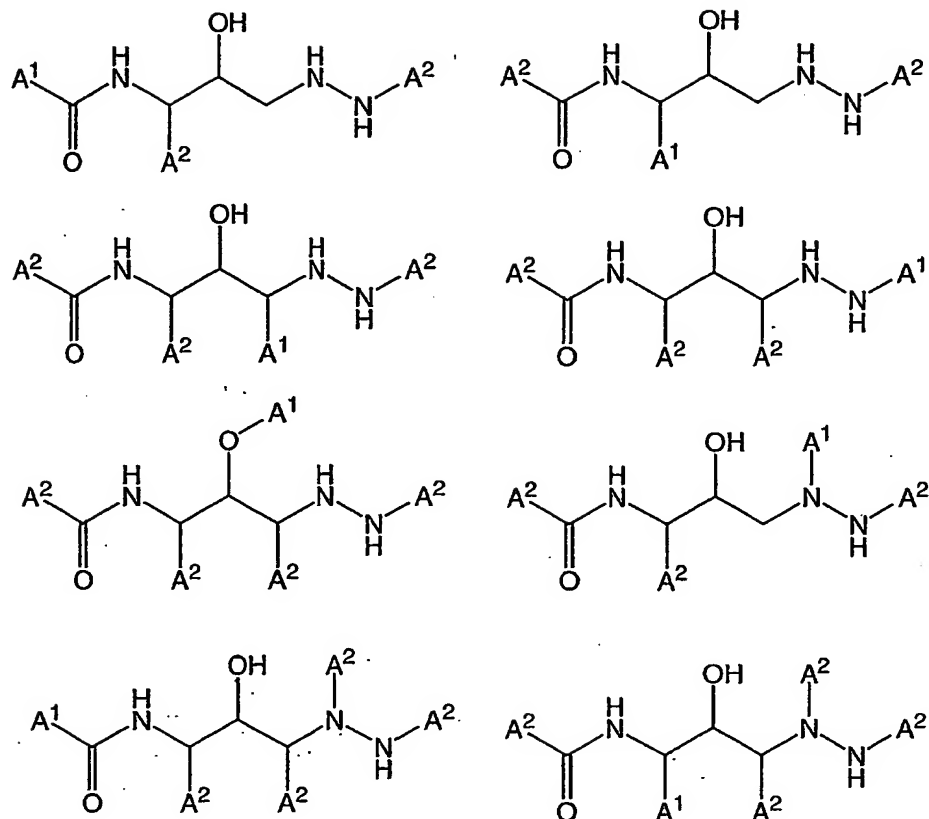
Exemplary embodiments of Formula V compounds include, but are not limited to, structures:



and

where A¹ denotes a covalent attachment site of a phosphonate group.

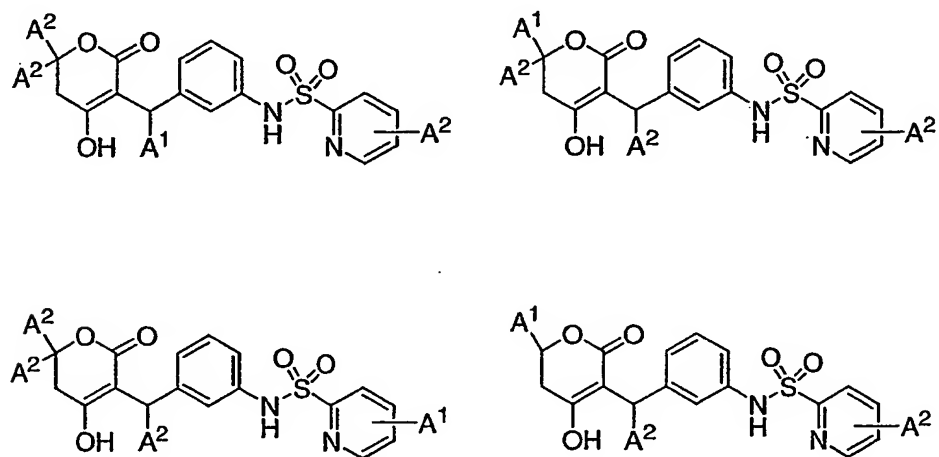
Exemplary embodiments of Formula VI compounds include, but are not limited to, structures:



where A¹ denotes a covalent attachment site of a phosphonate group.

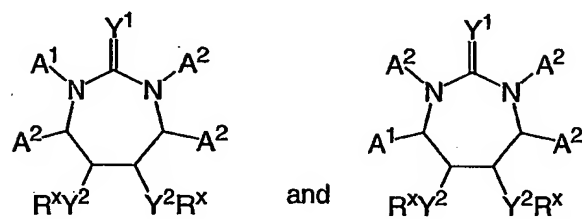
Exemplary embodiments of Formula VII compounds include, but are not limited to, structures:

5



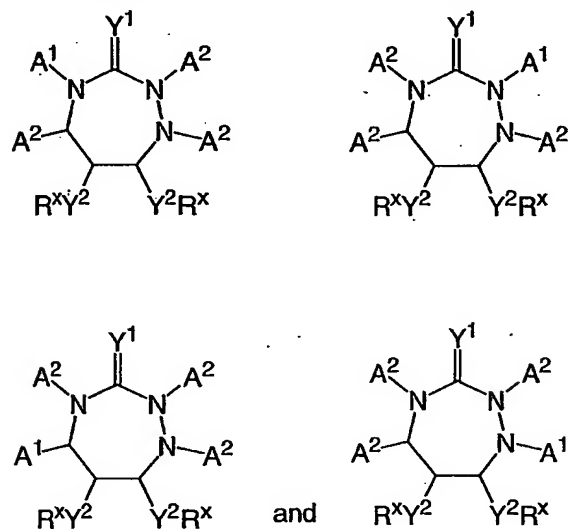
where A¹ denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula VIIIa compounds include structures:

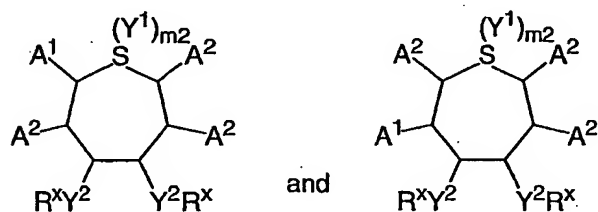


5

Exemplary embodiments of Formula VIIIb compounds include structures:

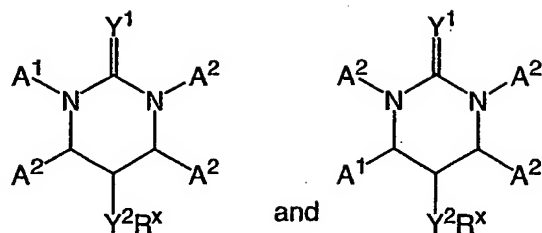


Exemplary embodiments of Formula VIIIc compounds include structures:



10

Exemplary embodiments of Formula VIId compounds include structures:



where A¹ denotes a covalent attachment site of a phosphonate group.

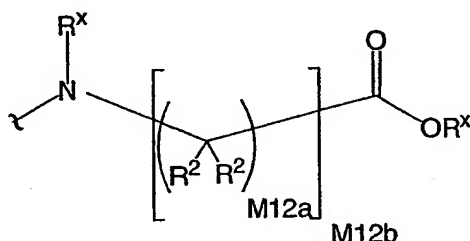
5 A Cellular Accumulation Embodiment

Another embodiment of the invention is directed toward an HIV protease inhibitor compound capable of accumulating in human PBMCs. Accumulation in human PBMCs is described in the examples herein. Typically, the compounds of this embodiment further
 10 comprise a phosphonate or phosphonate prodrug. More typically, the phosphonate or phosphonate prodrug has the structure A³ as described herein. Each of the preferred embodiments of A³ described herein is a preferred embodiment of A³ in the present embodiment.

Optionally, the compounds of this embodiment demonstrate improved intracellular
 15 half-life of the compounds or intracellular metabolites of the compounds in human PBMCs when compared to analogs of the compounds not having the phosphonate or phosphonate prodrug. Typically, the half-life is improved by at least about 50%, more typically at least in the range 50-100%, still more typically at least about 100%, more typically yet greater than about 100%.

20 In a preferred embodiment, the intracellular half-life of a metabolite of the compound in human PBMCs is improved when compared to an analog of the compound not having the phosphonate or phosphonate prodrug. In such embodiments, the metabolite is typically generated intracellularly, more typically, it is generated within human PBMCs. Still more typically, the metabolite is a product of the cleavage of a phosphonate prodrug within human
 25 PBMCs. More typically yet, the phosphonate prodrug is cleaved to form a metabolite having at least one negative charge at physiological pH. Most typically, the phosphonate prodrug is enzymatically cleaved within human PBMCs to form a phosphonate having at least one active hydrogen atom of the form P-OH.

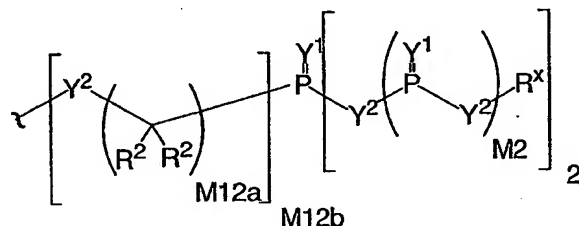
Notwithstanding other disclosure herein which describes the role or presents of phosphonates in the compounds of the invention, in another embodiment of the invention A^3 is A^{3a} which is of the formula:



5

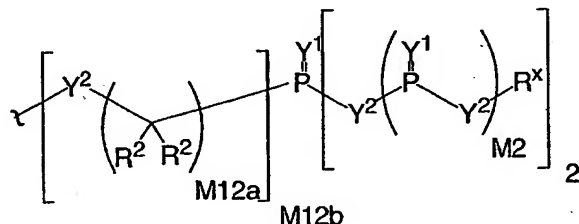
In this embodiment of the invention, any A^3 group may be A^{3a} .

In another aspect of the invention, A^3 is of the formula:



- 10 M12a is other than 0 and at least one phosphonate group present in the compound is not bonded directly to W^3 . More typically, the phosphonate is not bonded directly to W^5 . In such an embodiment, the phosphorous atom of the phosphonate is not bonded directly to a carbon atom of a ring.

- 15 In another aspect of the invention an Amprenavir like phosphonate protease inhibitor, as described above in the description and below in the claims, contains an A^3 group of the formula:

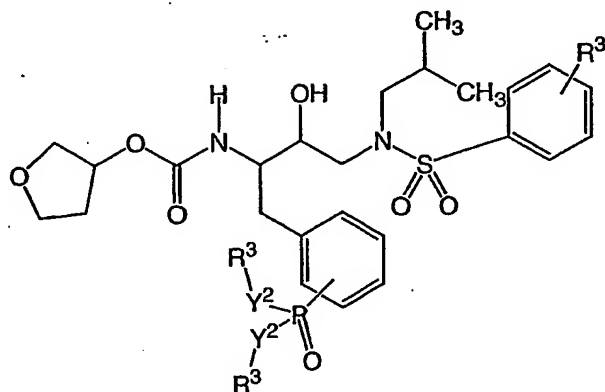


M12a is other than 0 and at least one phosphonate group present in the compound is not bonded directly to W^3 . More typically, the phosphonate is not bonded directly to W^5 . In

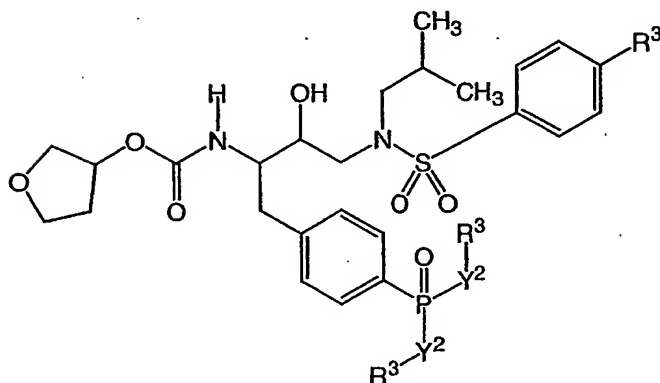
such an embodiment, the phosphorous atom of the phosphonate is not bonded directly to a carbon atom of a ring.

One embodiment of Amprenavir like phosphonate protease inhibitors as described above in the description and below in the claims excludes compounds of the formulas:

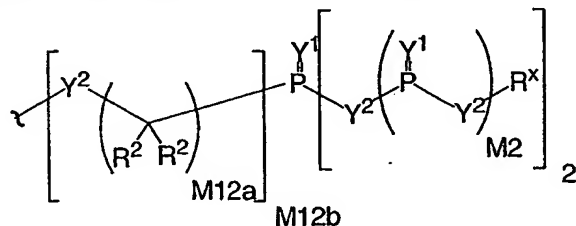
5



or

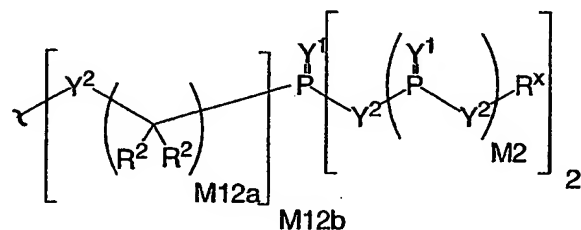


In another aspect of the invention, A³ is of the formula:



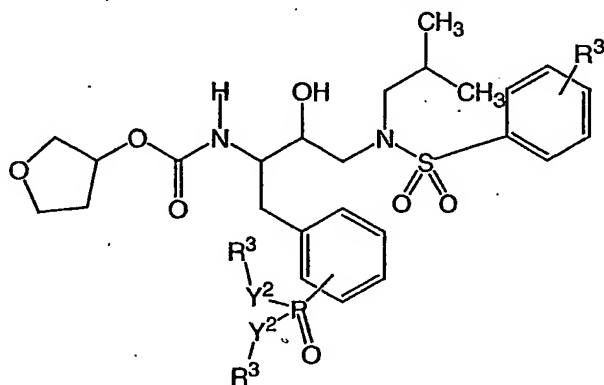
- 10 M12a is 0 and at least one phosphonate group present in the compound is bonded directly to W³. More typically, the phosphonate is bonded directly to W⁵. In such an embodiment, the phosphorous atom of the phosphonate is bonded directly to a carbon atom of a ring.

In another aspect of the invention an Amprenavir like phosphonate protease inhibitor, as described above in the description and below in the claims, contains an A³ group of the formula:

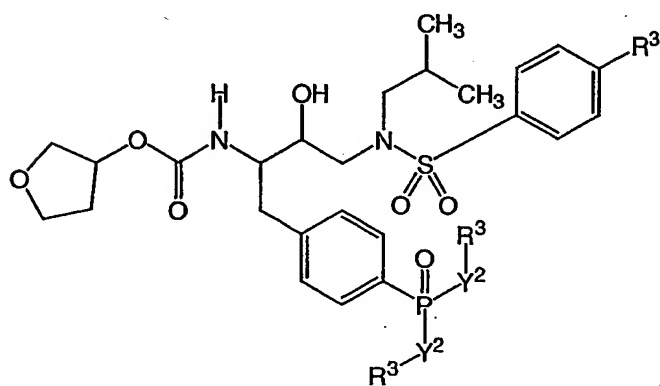


- 5 M12a is 0 and at least one phosphonate group present in the compound is bonded directly to W³. More typically, the phosphonate is bonded directly to W⁵. In such an embodiment, the phosphorous atom of the phosphonate is bonded directly to a carbon atom of a ring.

One embodiment of Amprenavir like phosphonate protease inhibitors as described above in the description and below in the claims is directed to compounds of the formulas:

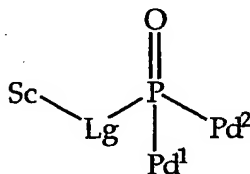


or



Exemplary Enumerated Compounds.

By way of example and not limitation, embodiments of the invention are named below in tabular format (Table 100). These embodiments are of the general formula "MBF":



MBF

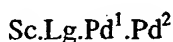
5

Each embodiment of MBF is depicted as a substituted nucleus (Sc) in which the nucleus is designated by a number and each substituent is designated in order by letter or number.

Tables 1.1 to 1.5 are a schedule of nuclei used in forming the embodiments of Table 100.

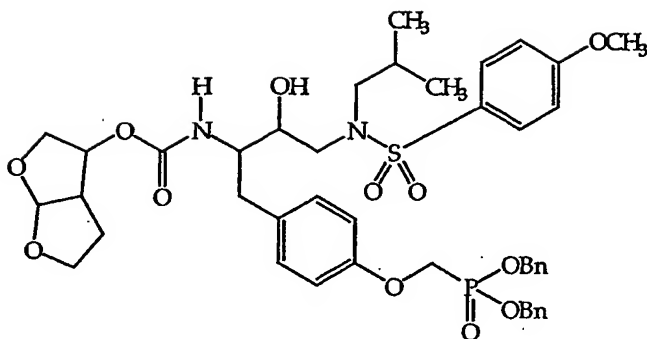
Each nucleus (Sc) is given a number designation from Tables 1.1 to 1.5, and this designation appears first in each embodiment name. Similarly, Tables 10.1 to 10.19 and 20.1 to 20.36 list the selected linking groups (Lg) and prodrug (Pd¹ and Pd²) substituents, again by letter or number designation, respectively.

Accordingly, each named embodiment of Table 100 is depicted by a number designating the nucleus from Table 1.1-1.5, followed by a letter designating the linking group (Lg) from Table 10.1-10.19, and two numbers designating the two prodrug groups (Pd¹ and Pd²) from Table 20.1-20.36. In graphical tabular form, each embodiment of Table 100 appears as a name having the syntax:



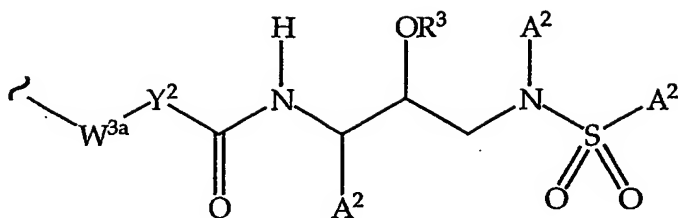
20

Thus, ignoring stereochemistry, structure 10, Scheme 2, Scheme Section A, is represented by 12.AH.247.247.

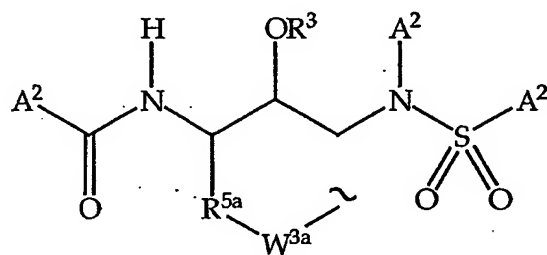


12.AH247.247

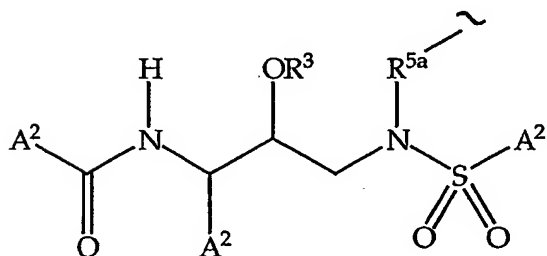
Each Sc group is shown having a tilde (“~”). The tilde is the point of covalent attachment of Sc to Lg. Q¹ and Q² of the linking groups (Lg), it should be understood, do not represent groups or atoms but are simply connectivity designations. Q¹ is the site of the covalent bond to the nucleus (Sc) and Q² is the site of the covalent bond to the phosphorous atom of formula MBF. Each prodrug group (Pd¹ and Pd²) are covalently bonded to the phosphorous atom of MBF at the tilde symbol (“~”). Some embodiments of Tables 10.1-10.19 and 20.1-20.36 may be designated as a combination of letters and numbers (Table 10.1-10.19) or number and letter (Table 20.1-20.36). For example there are Table 10 entries for BJ1 and BJ2. In any event, entries of Table 10.1-10.19 always begin with a letter and those of Table 20.1-20.36 always begin with a number. When a nucleus (Sc) is shown enclosed within square brackets (“[]”) and a covalent bond extends outside the brackets, the point of covalent attachment of Sc to Lg may be at any substitutable site on SC. Selection of the point of attachment is described herein. By way of example and not limitation, the point of attachment is selected from those depicted in the schemes and examples.

Table 1.1

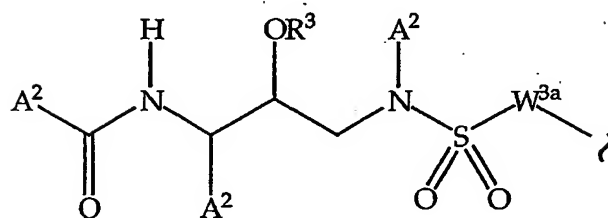
1



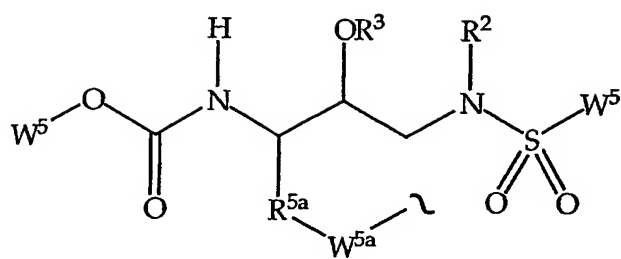
2



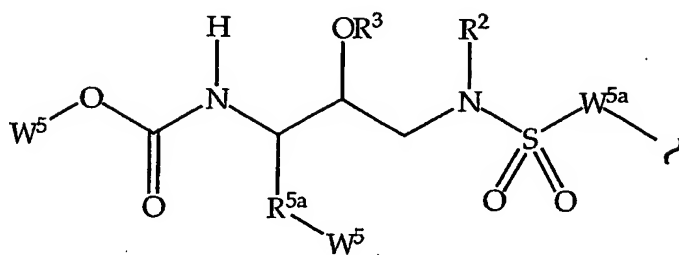
3



4

Table 1.2

5



6

Table 1.3

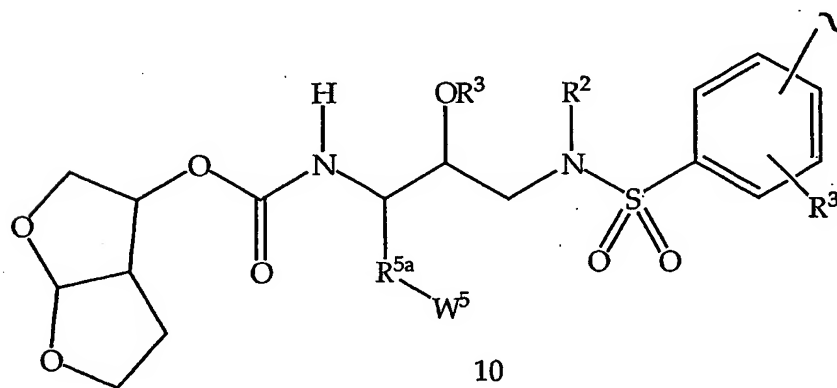
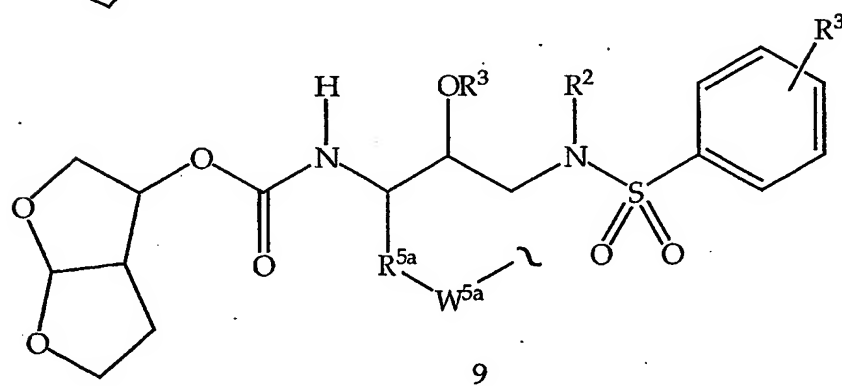
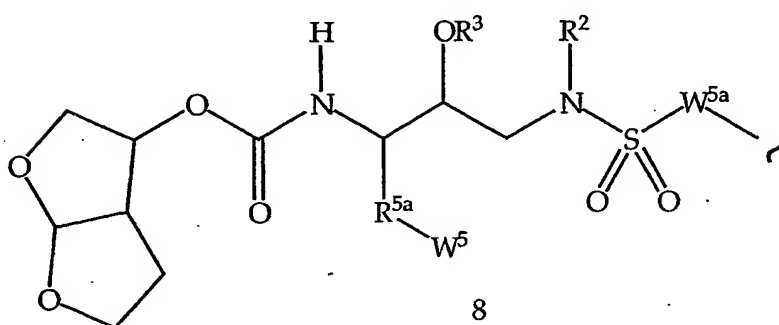
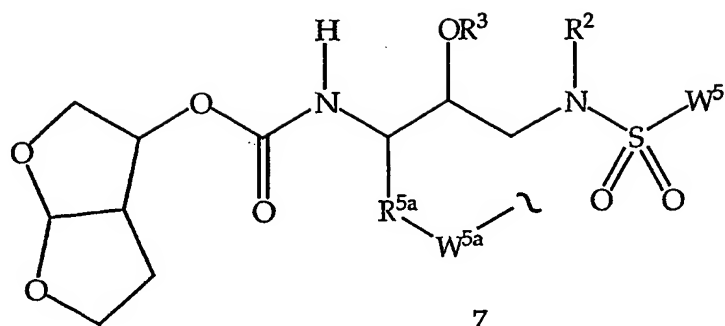


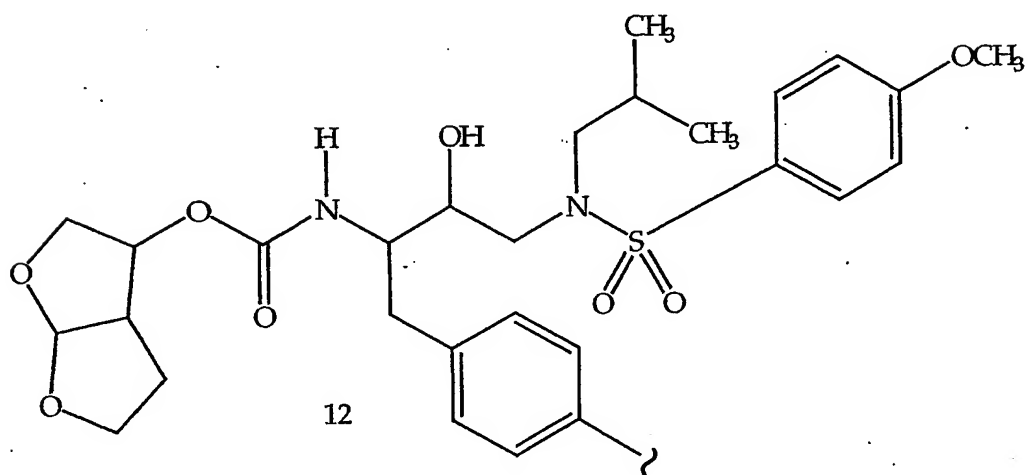
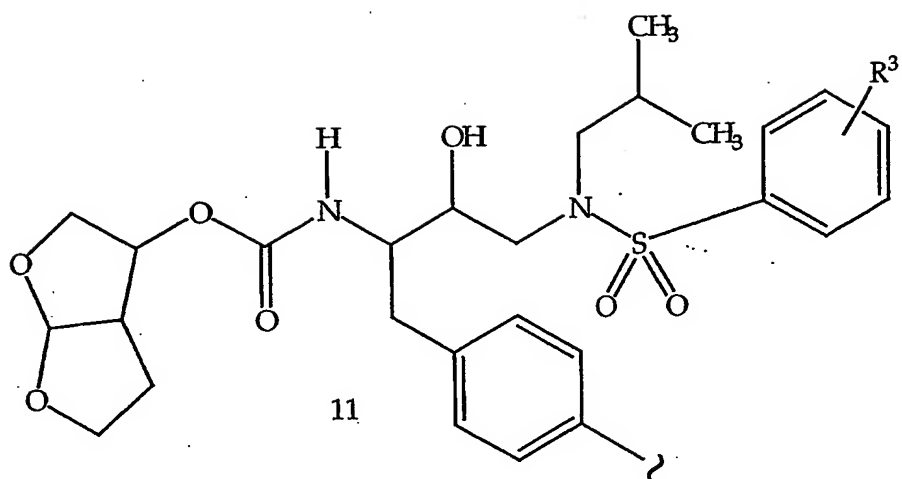
Table 1.4

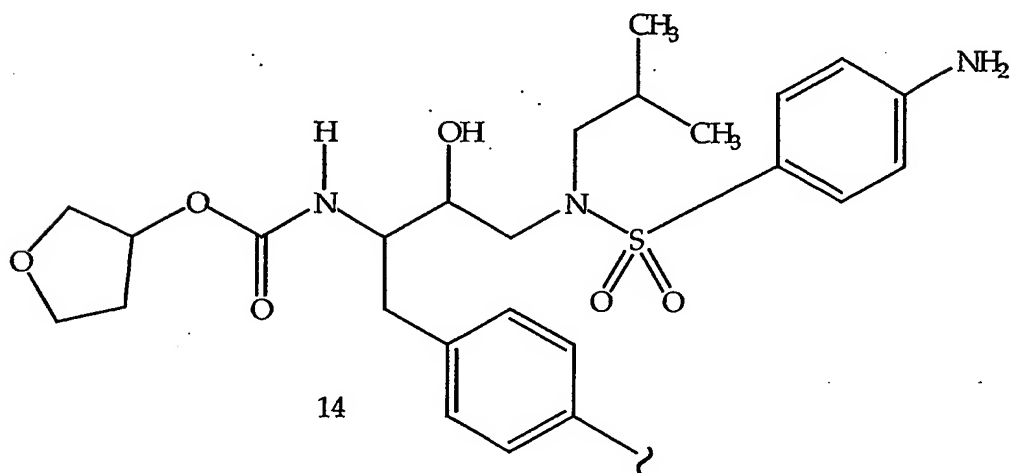
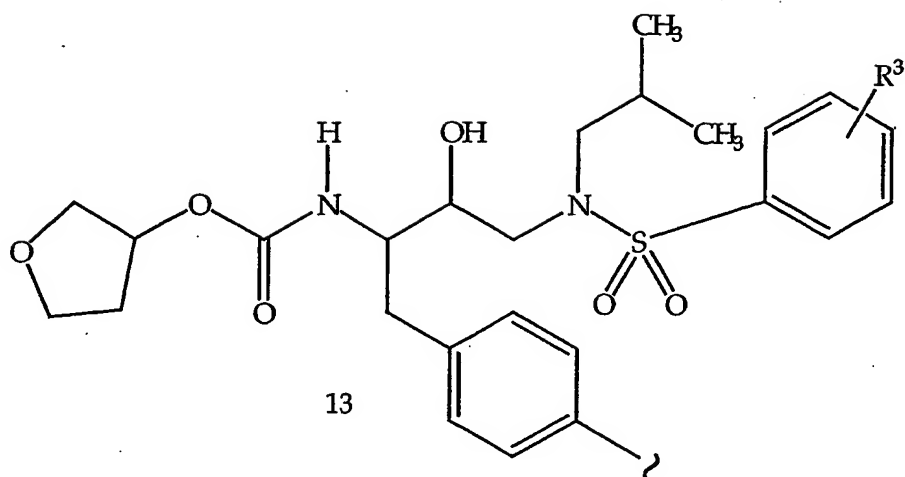
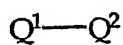
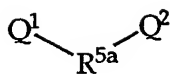
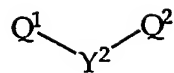
Table 1.5

Table 10.1

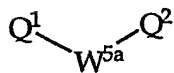
A



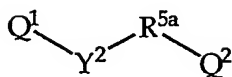
B



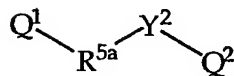
C



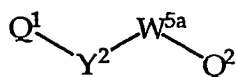
D



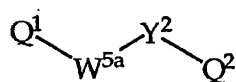
E



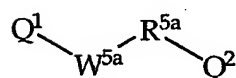
F



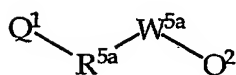
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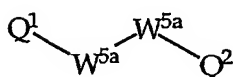
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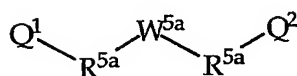
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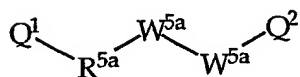
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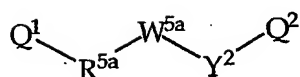
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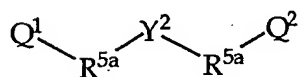
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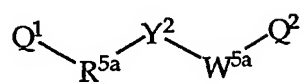
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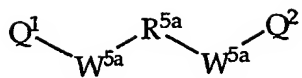
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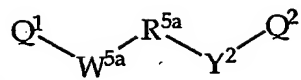
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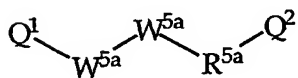
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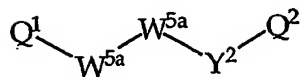
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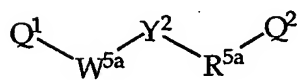
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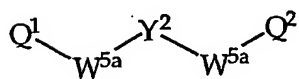
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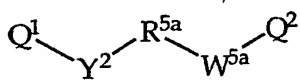
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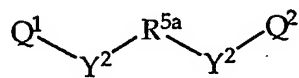
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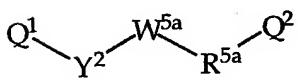
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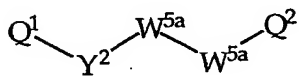
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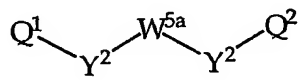
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Y



Z



AA

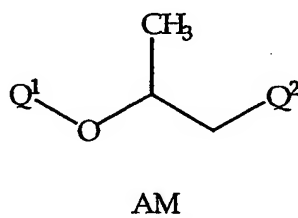
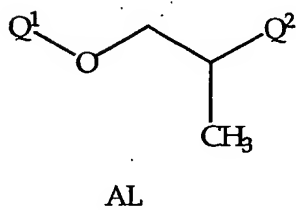
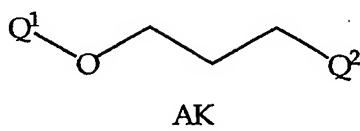
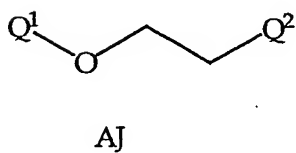
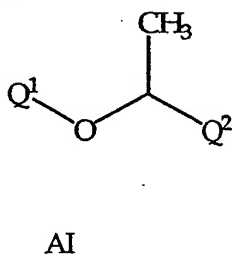
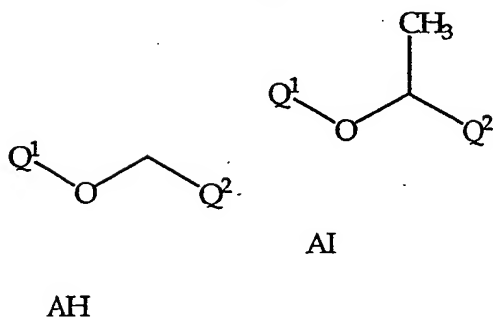
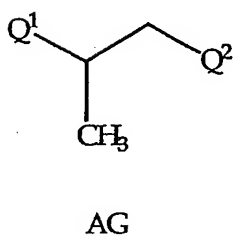
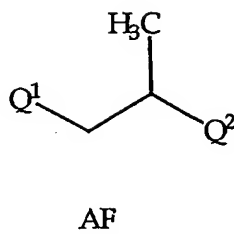
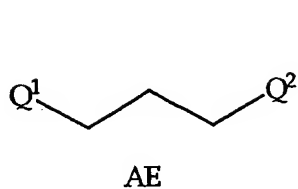
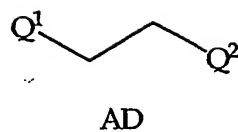
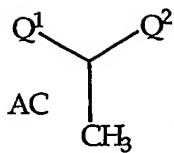
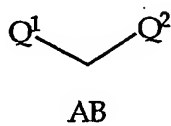
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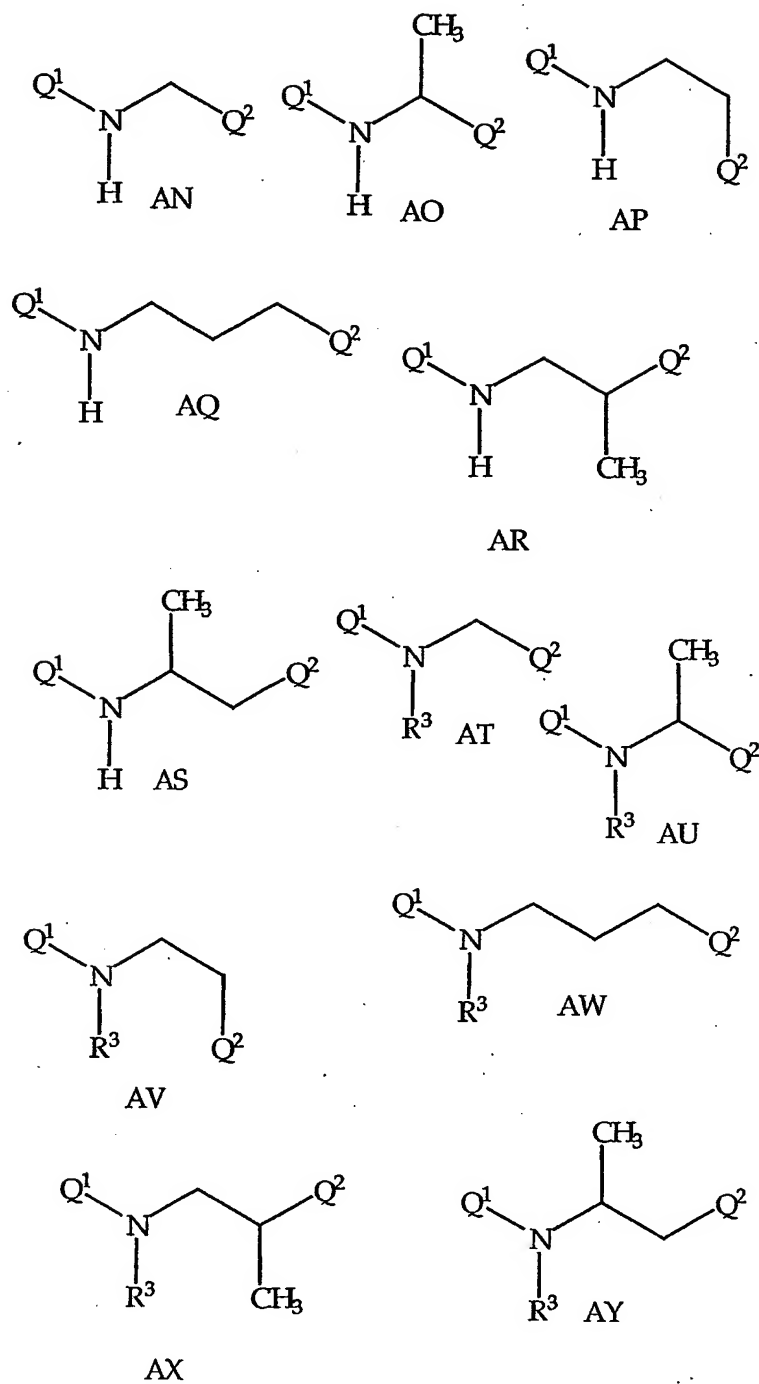
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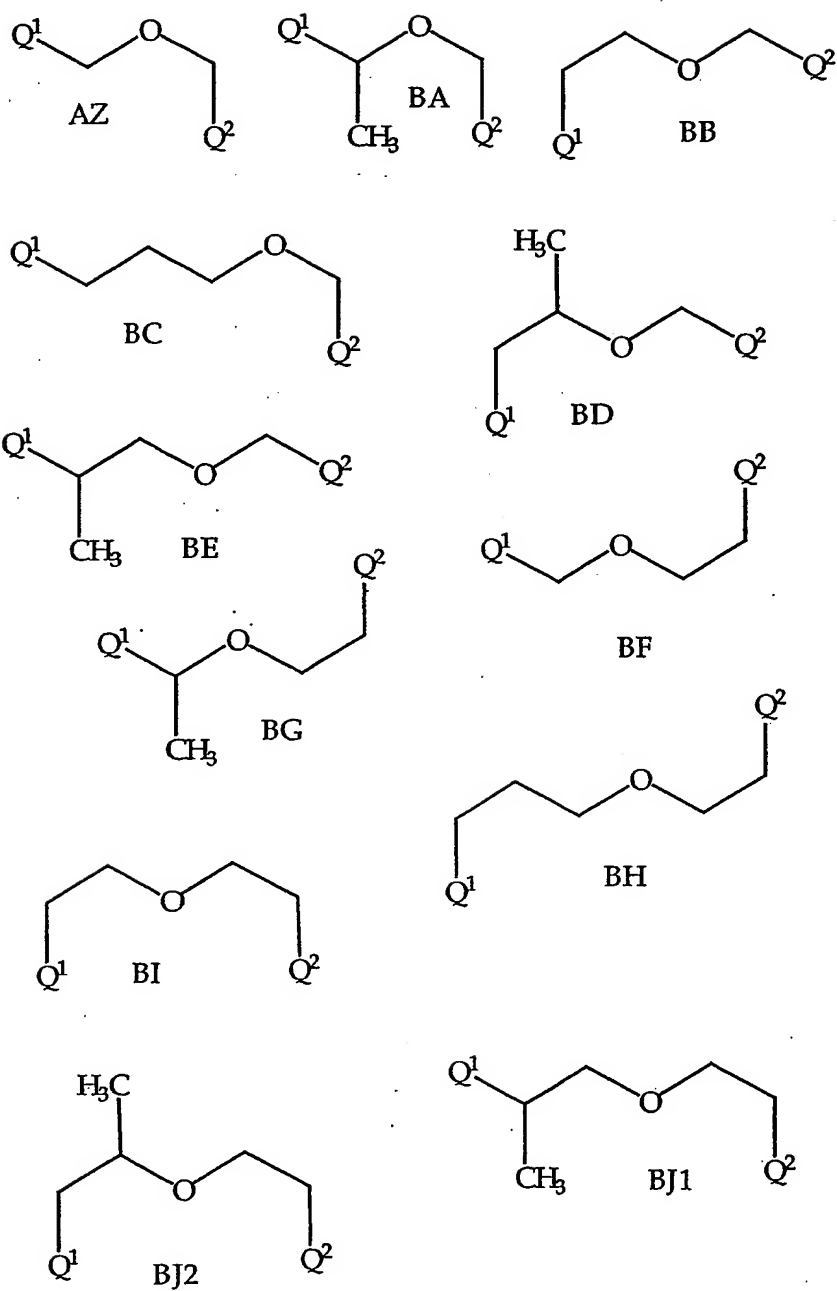
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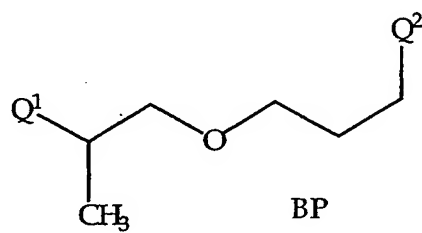
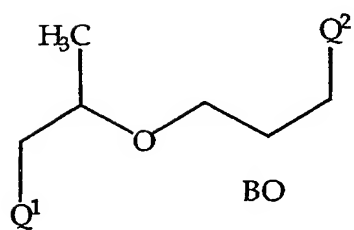
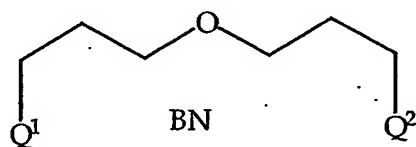
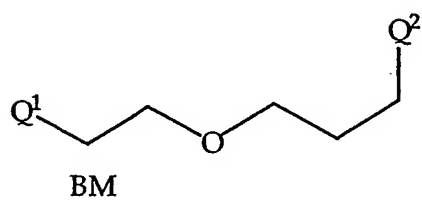
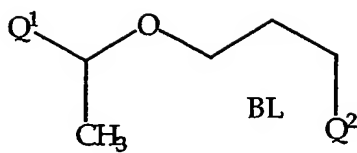
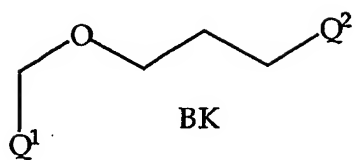
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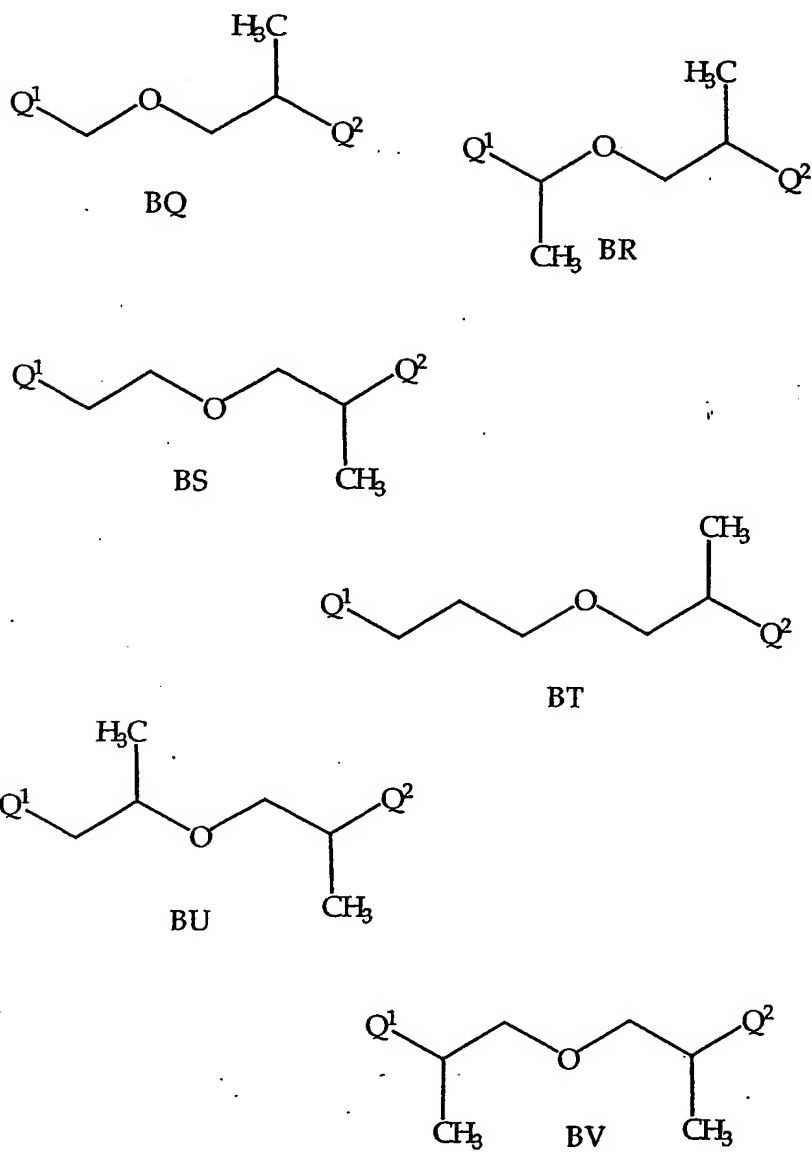
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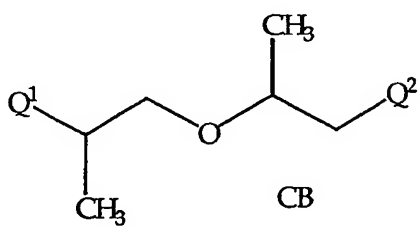
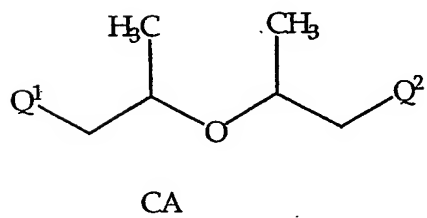
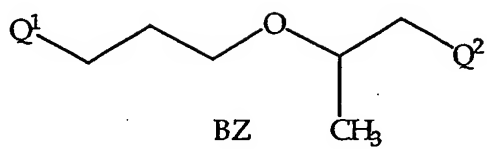
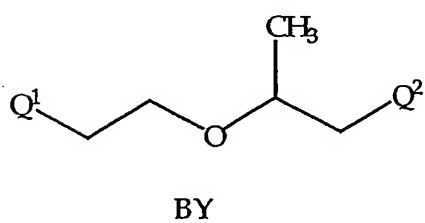
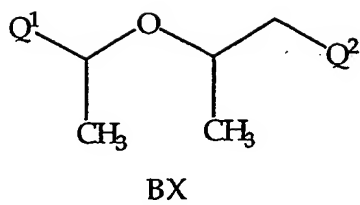
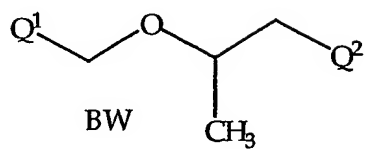
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Table 10.9

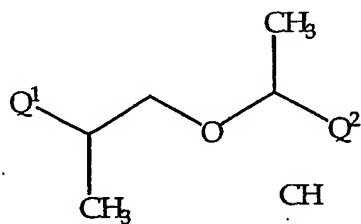
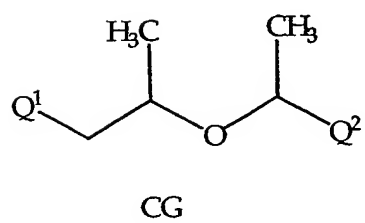
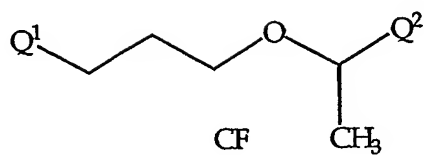
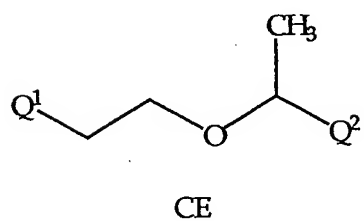
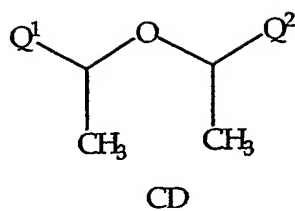
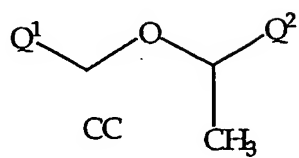


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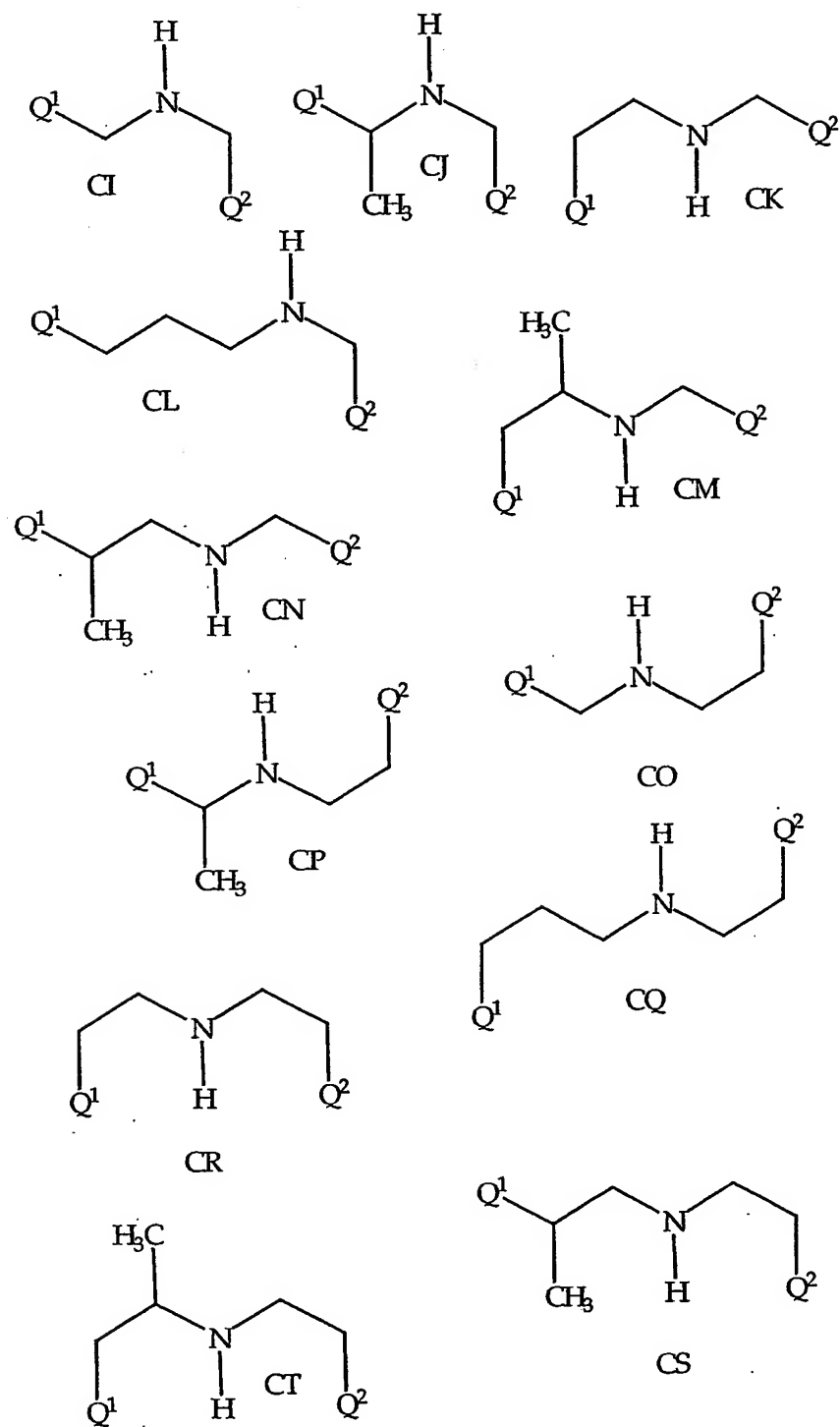


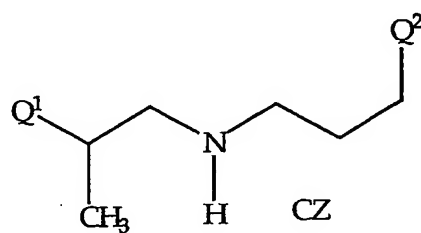
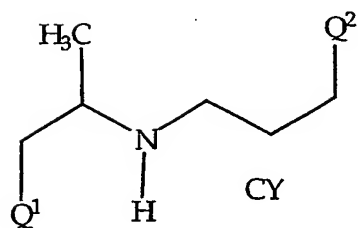
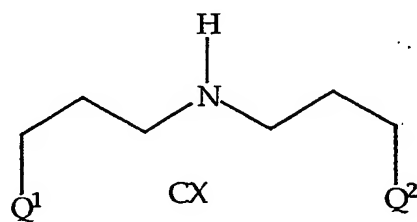
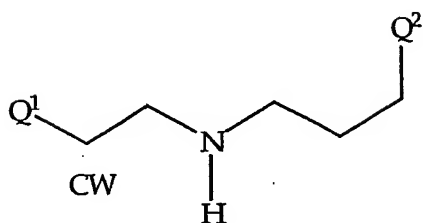
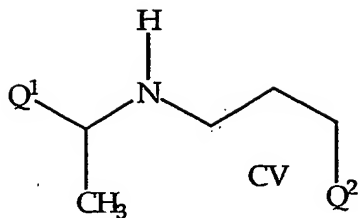
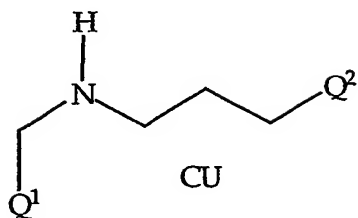
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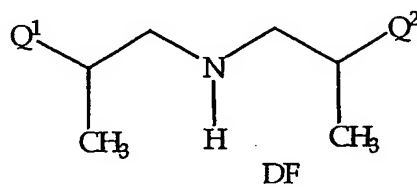
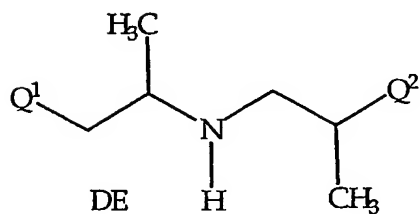
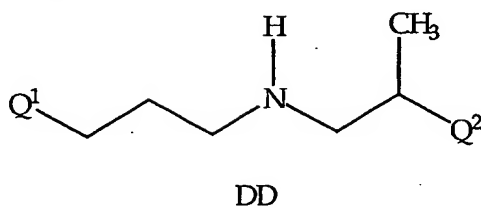
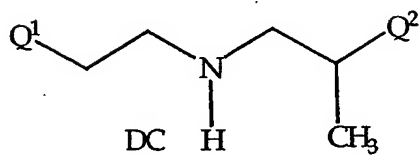
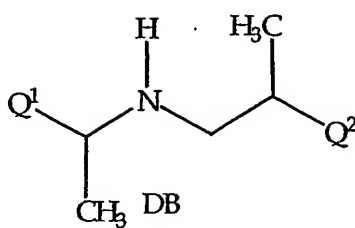
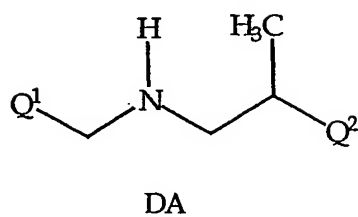
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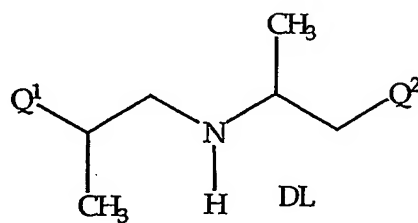
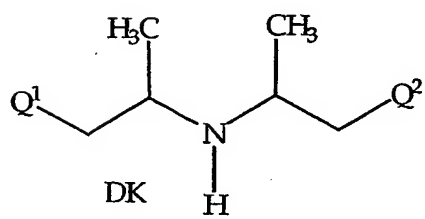
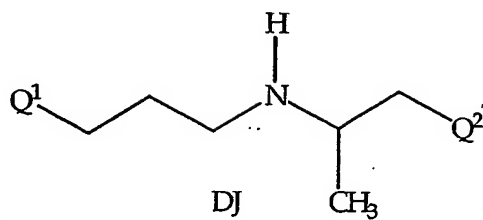
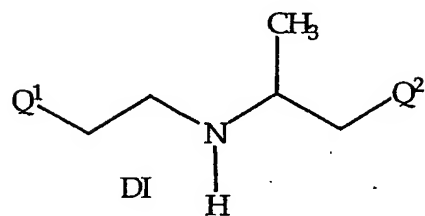
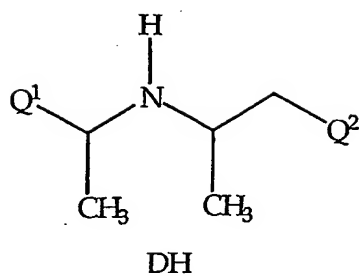
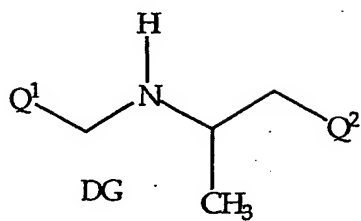
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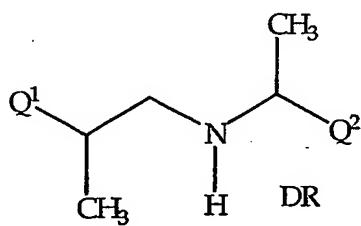
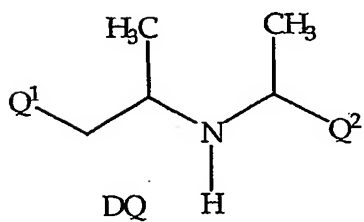
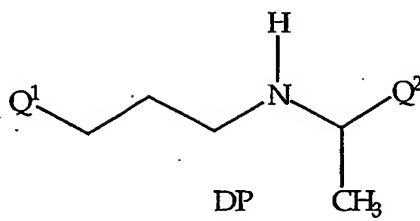
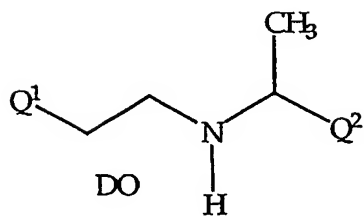
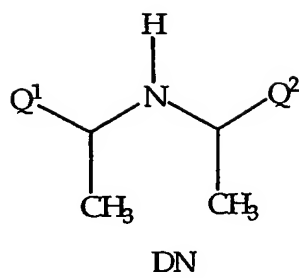
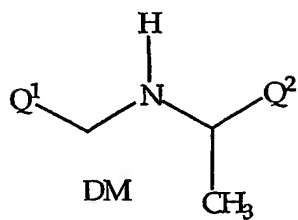
Table 10.14

Table 10.15

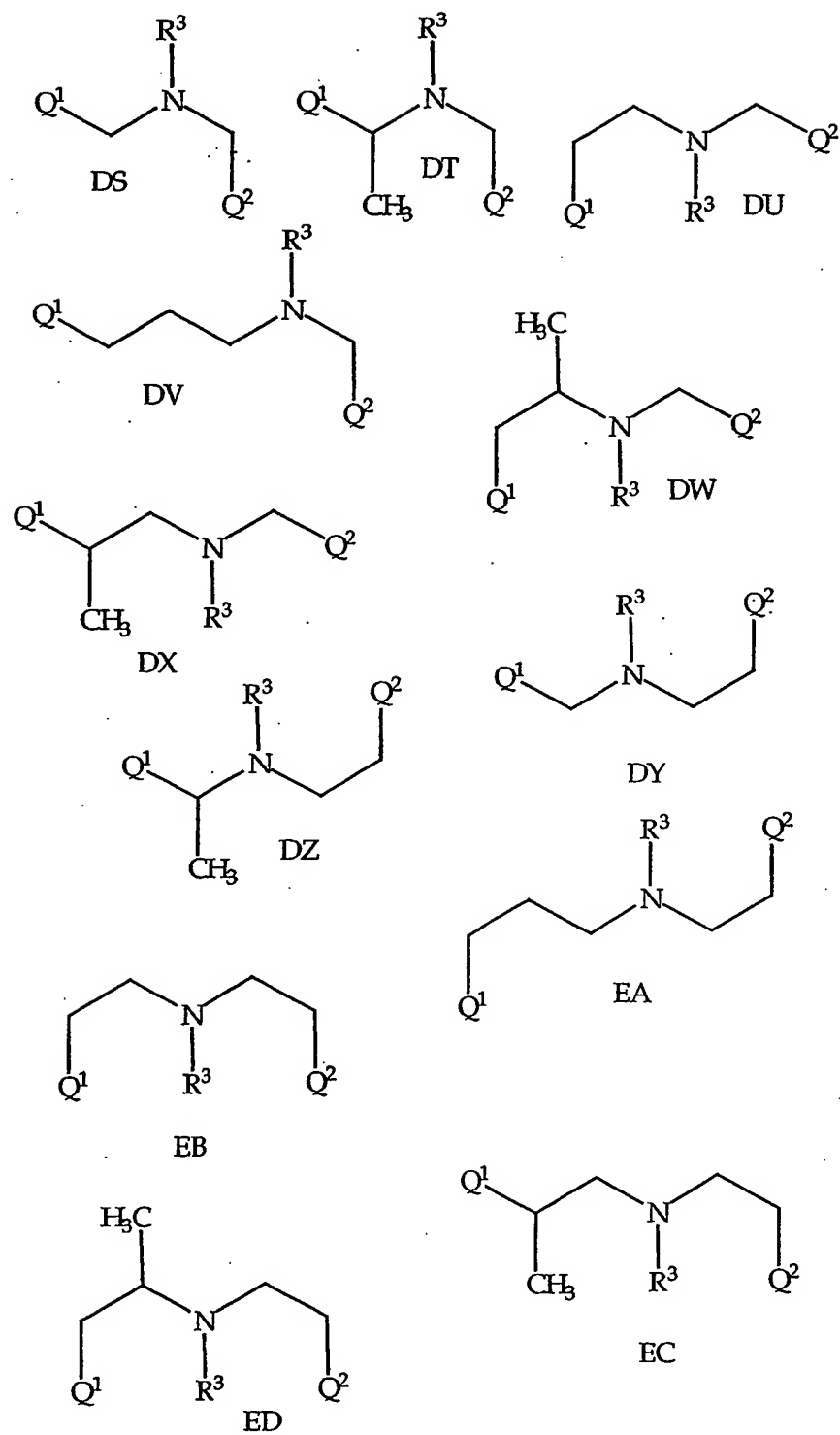


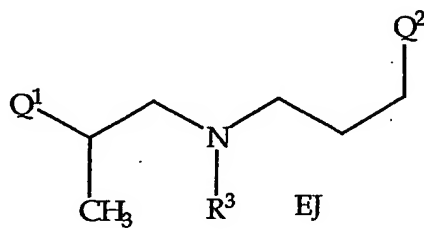
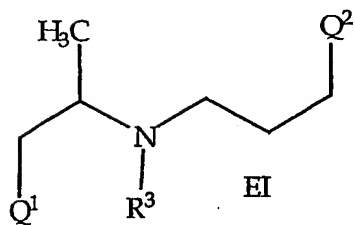
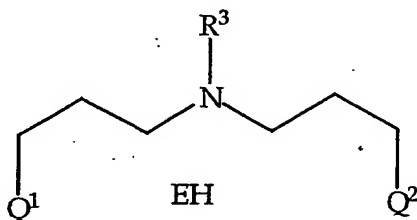
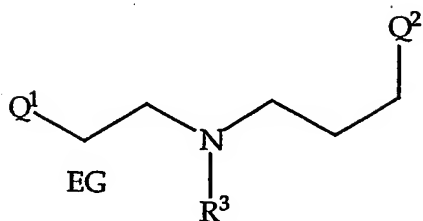
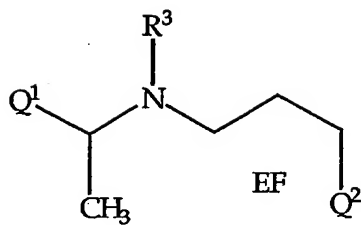
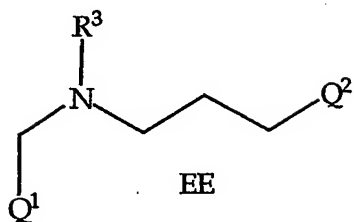
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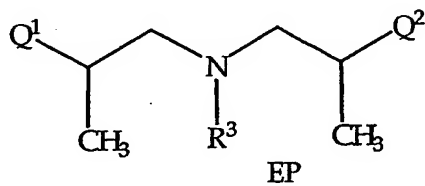
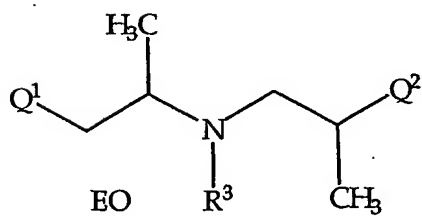
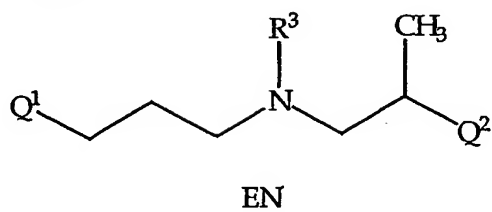
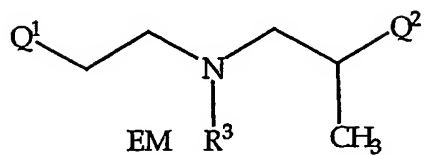
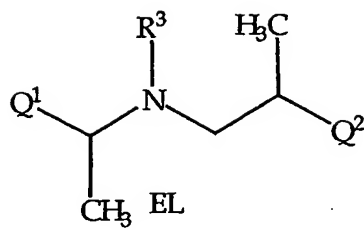
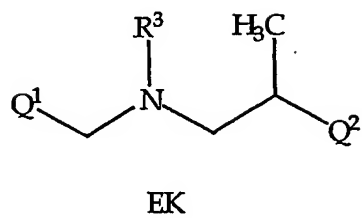
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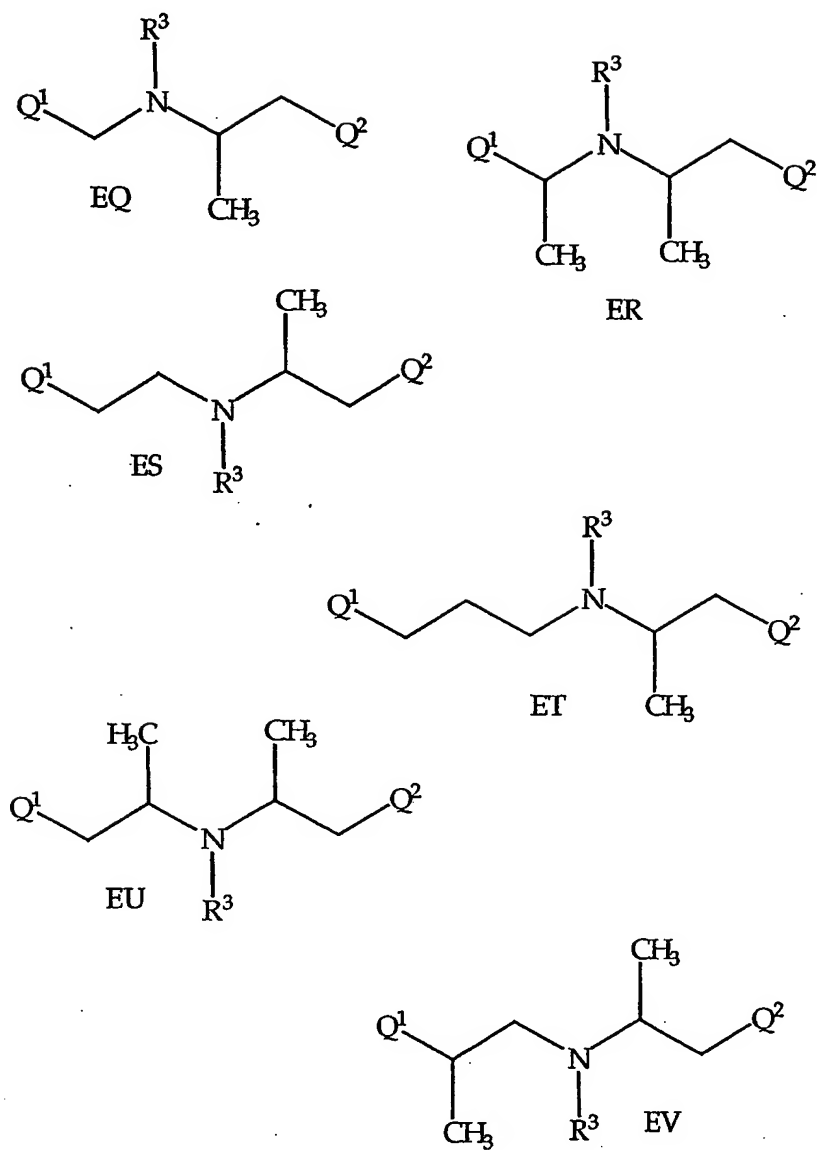
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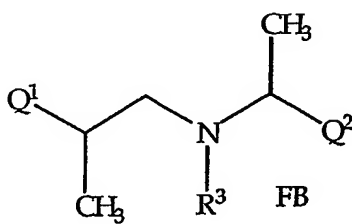
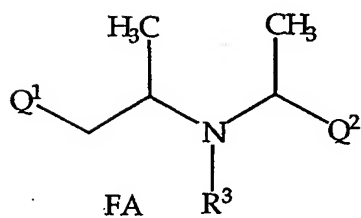
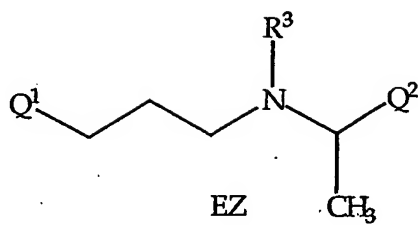
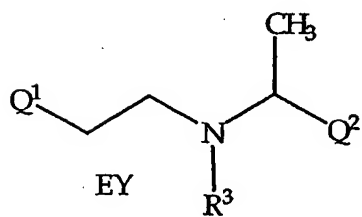
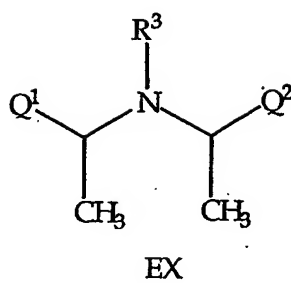
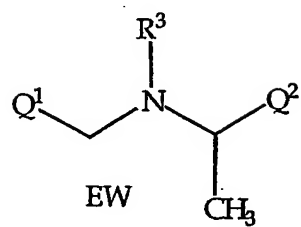
Table 10.19

Table 20.1

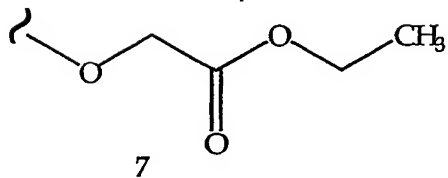
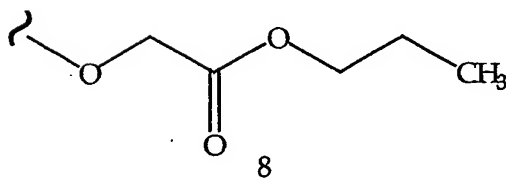
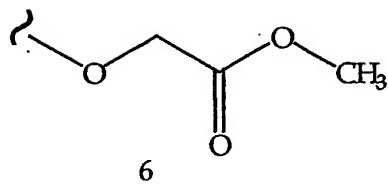
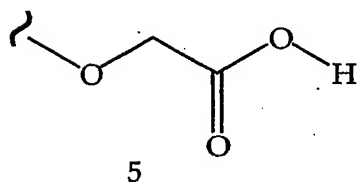
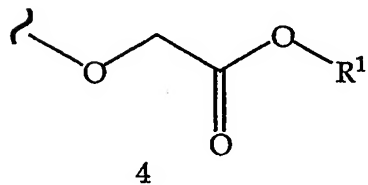
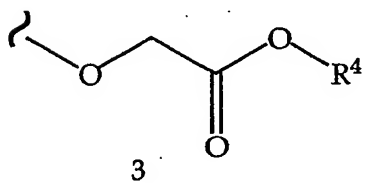
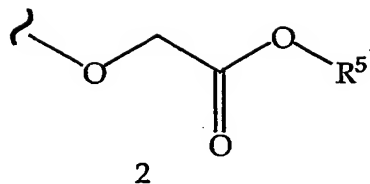
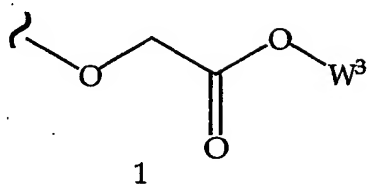


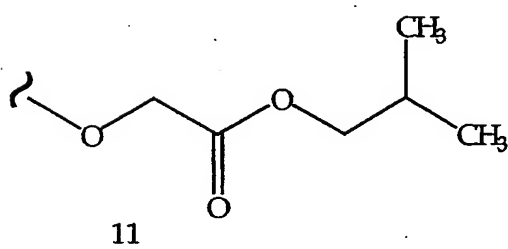
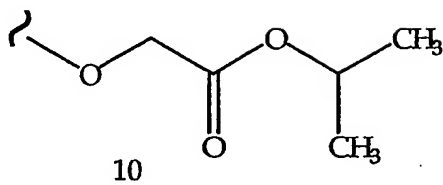
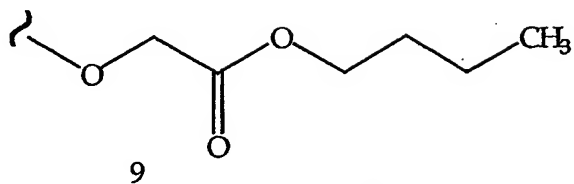
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Table 20.3

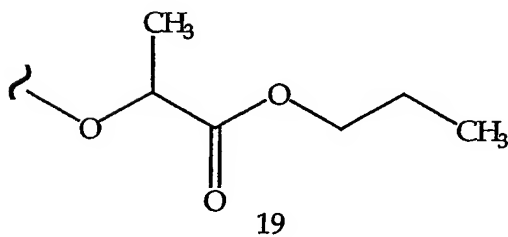
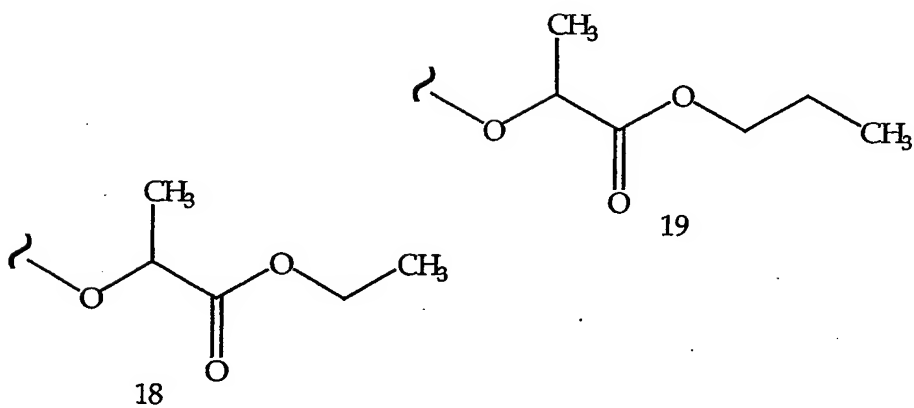
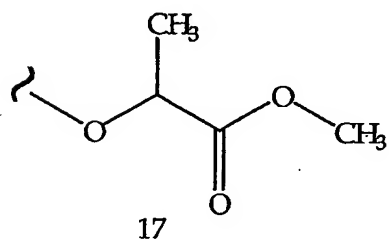
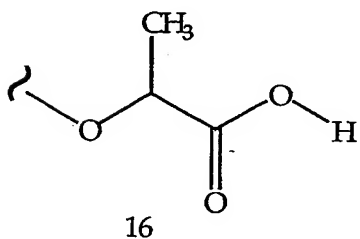
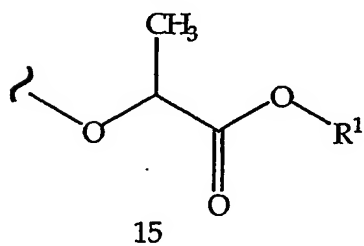
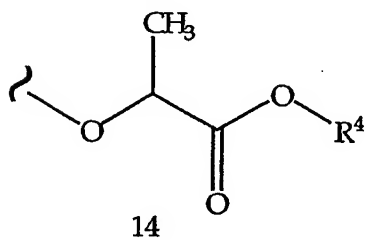
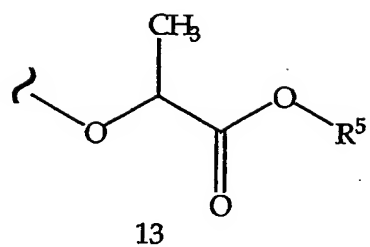
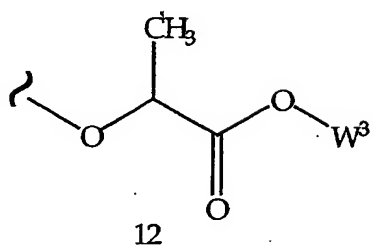


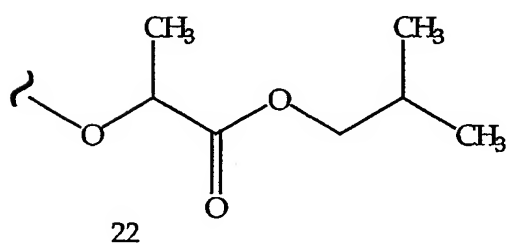
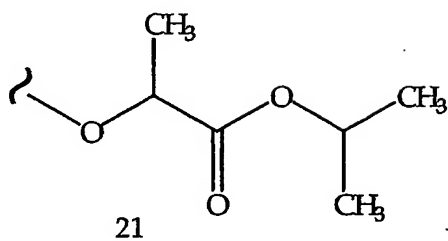
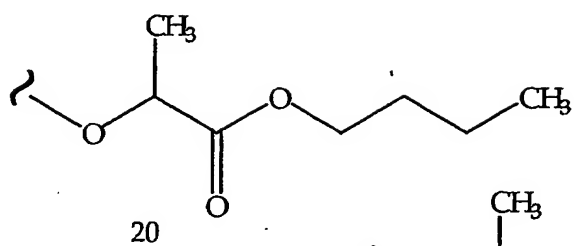
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Table 20.5

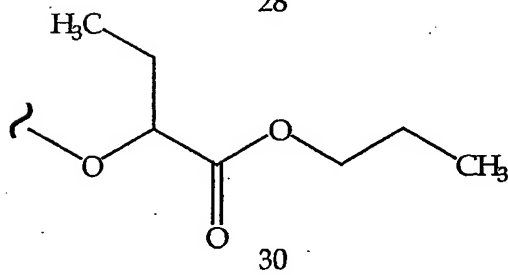
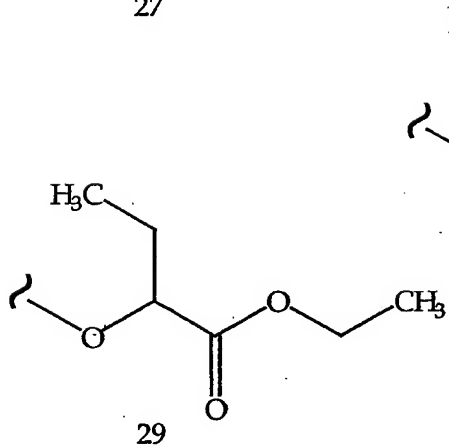
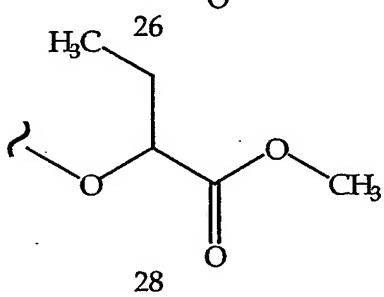
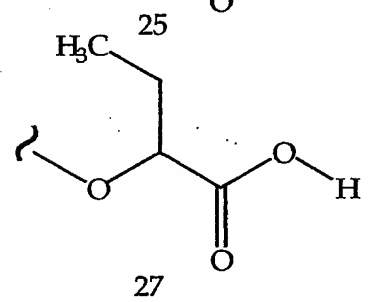
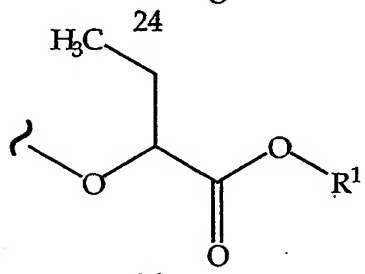
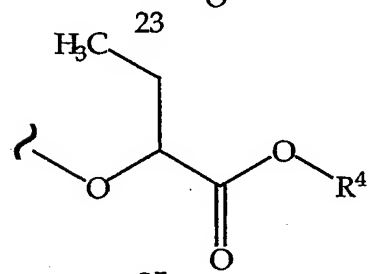
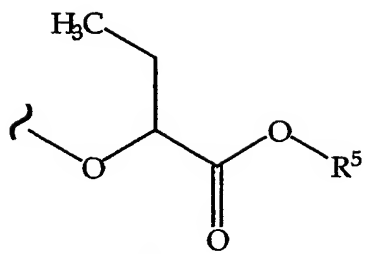
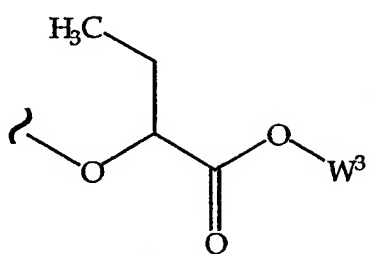


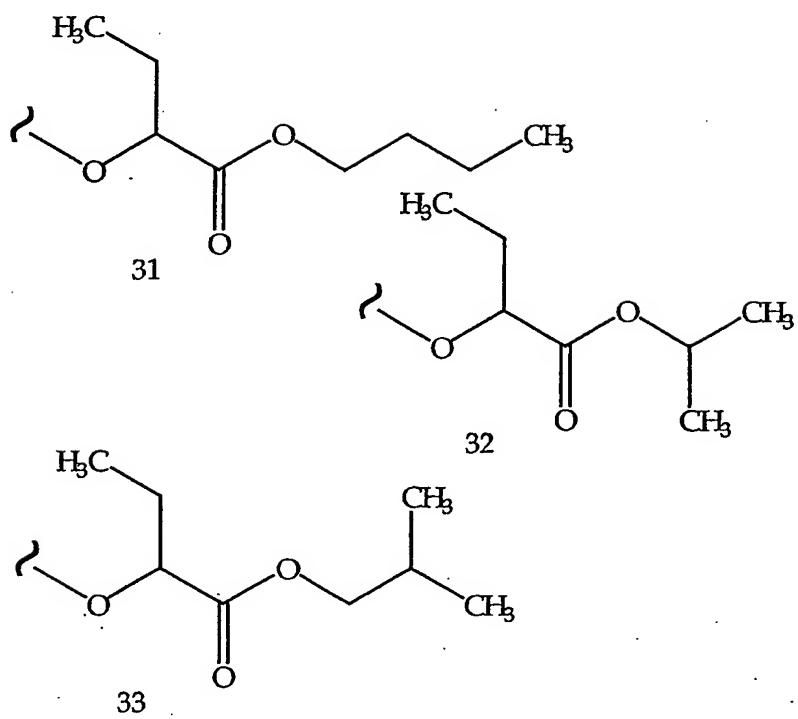
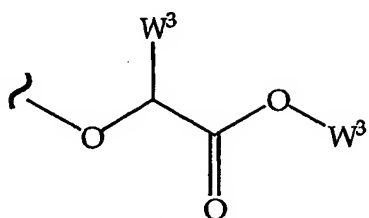
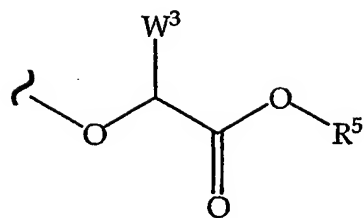
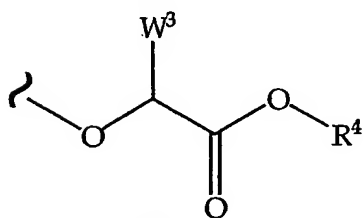
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Table 20.7

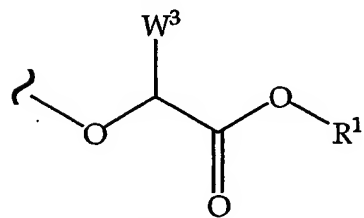
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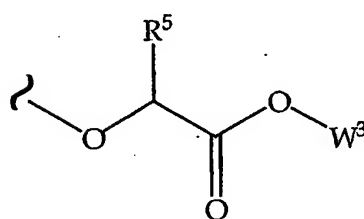
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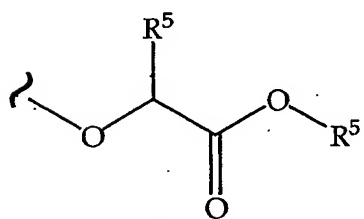
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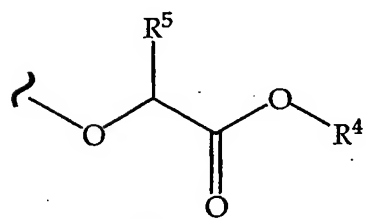
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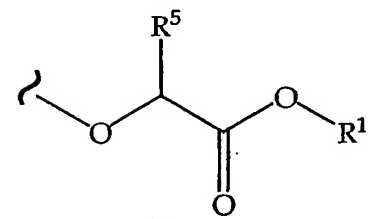
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39



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41

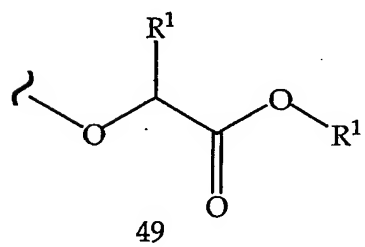
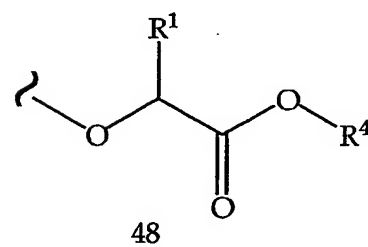
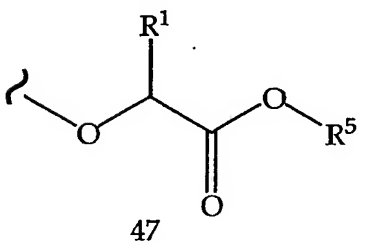
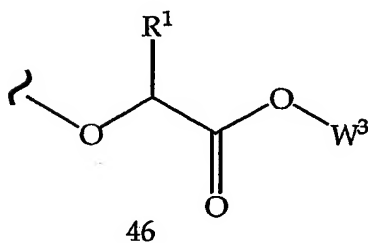
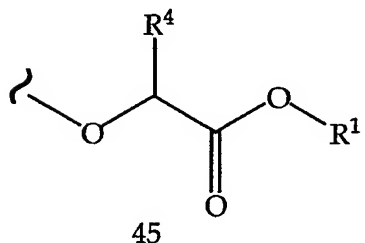
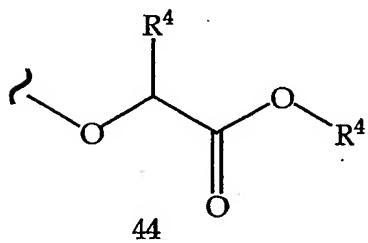
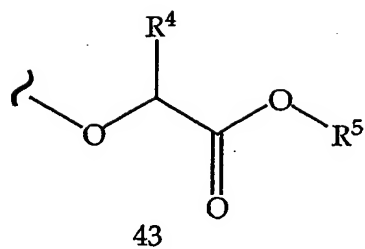
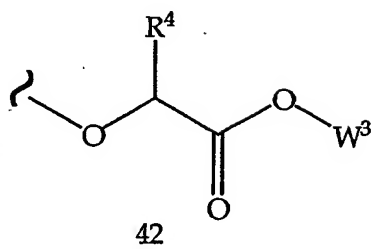
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Table 20.9

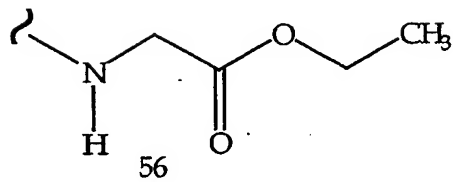
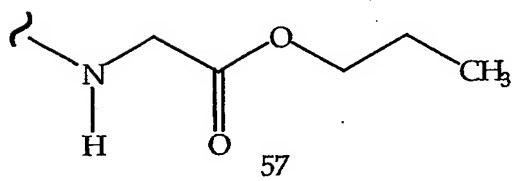
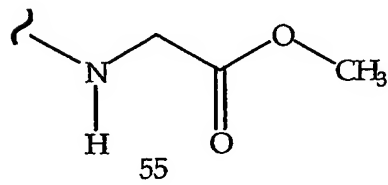
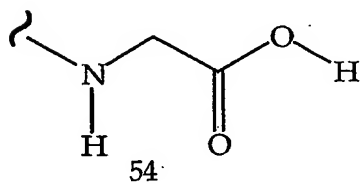
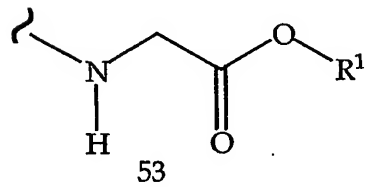
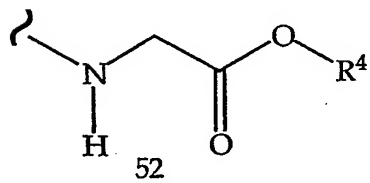
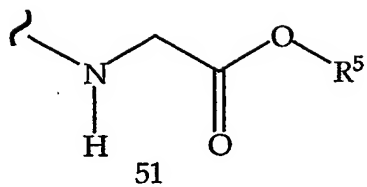
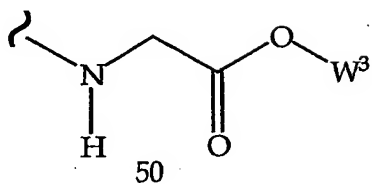


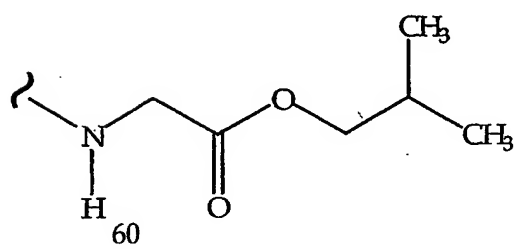
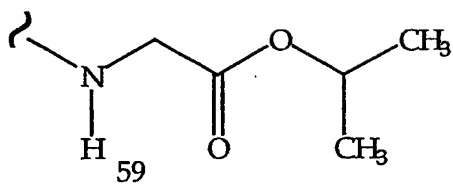
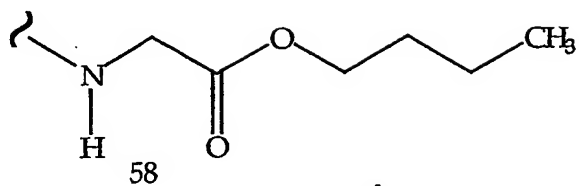
Table 20.10

Table 20.11

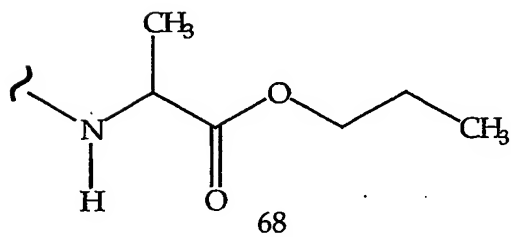
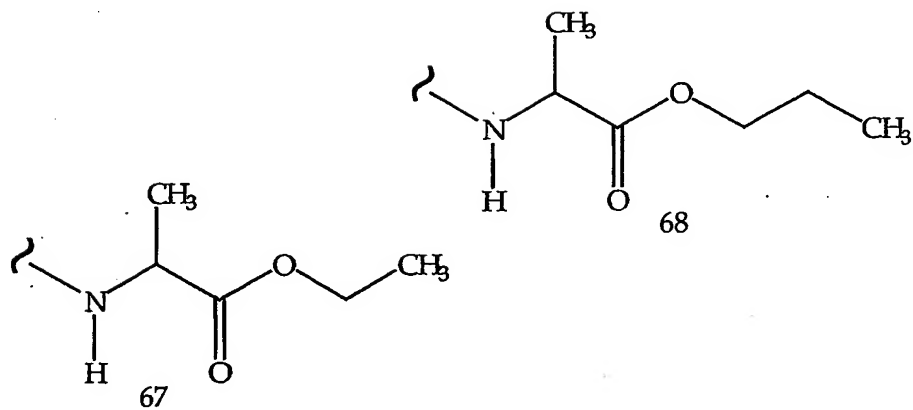
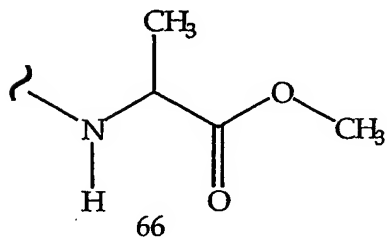
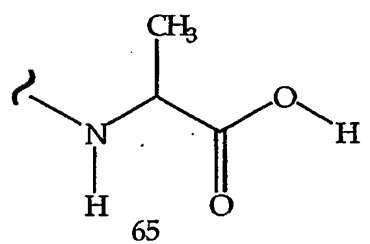
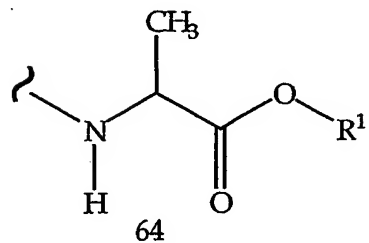
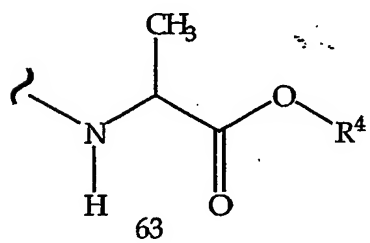
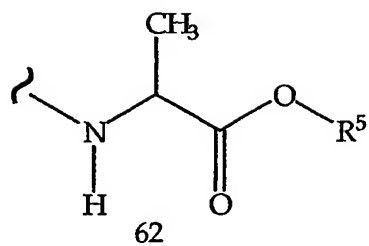
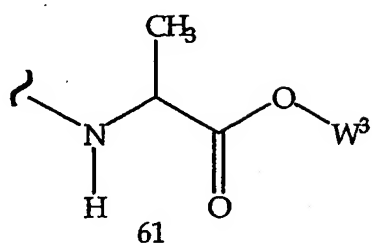


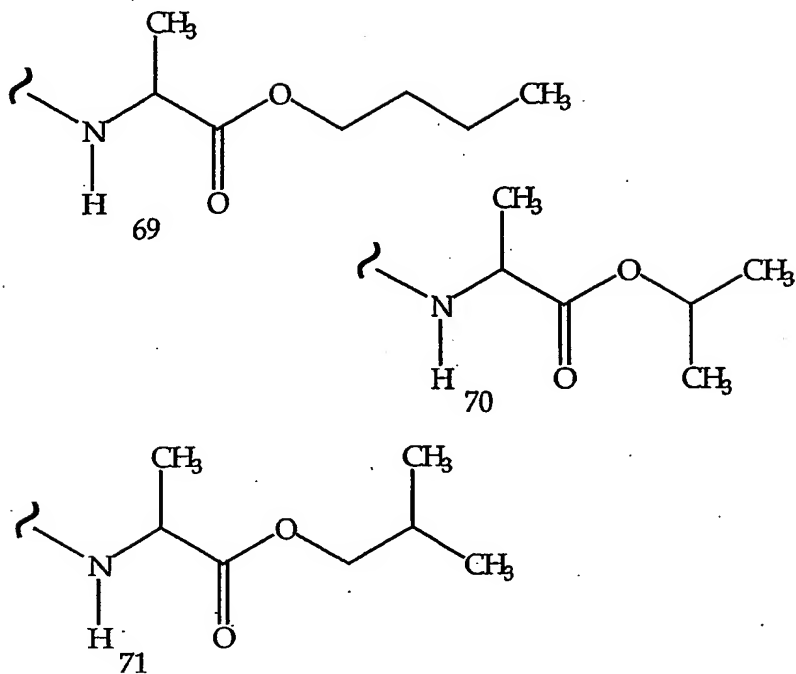
Table 20.12

Table 20.13

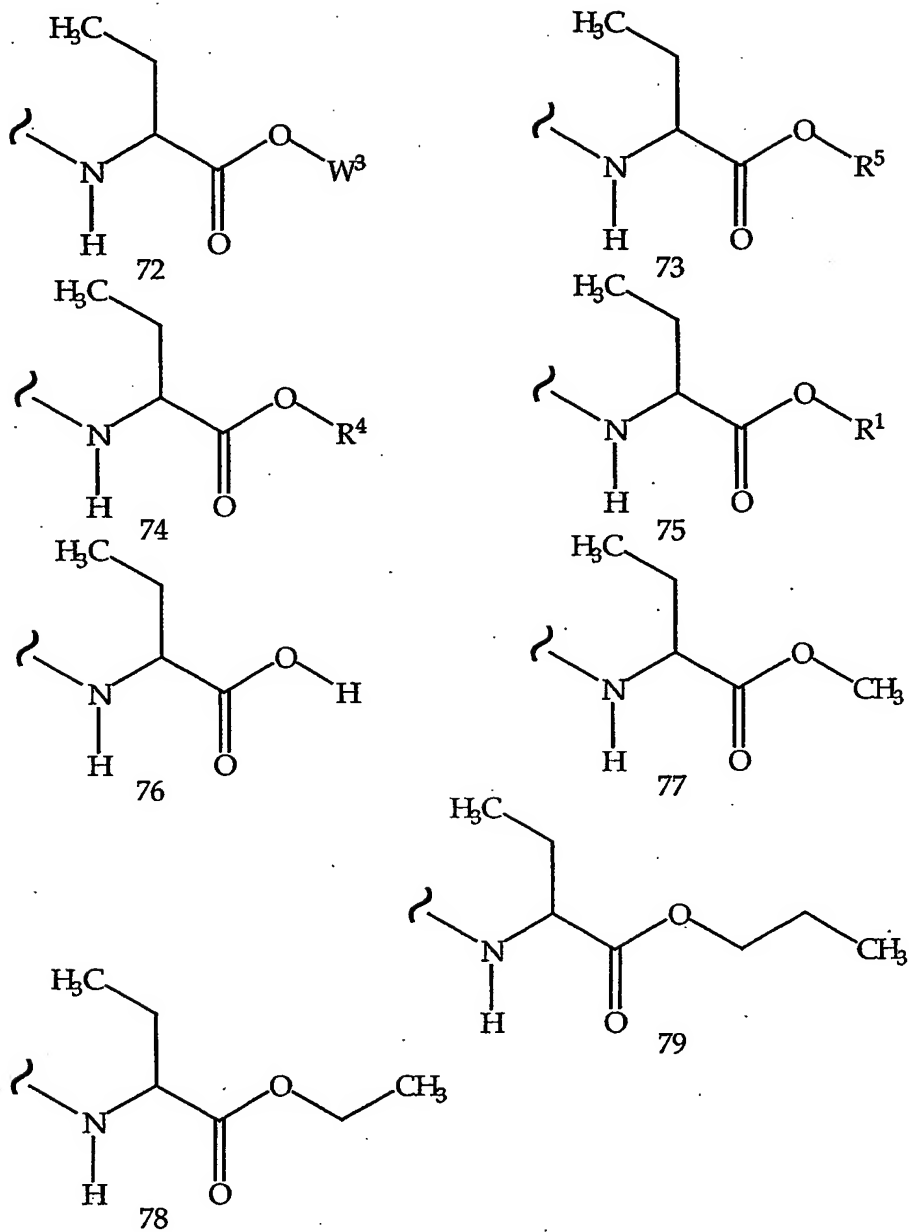


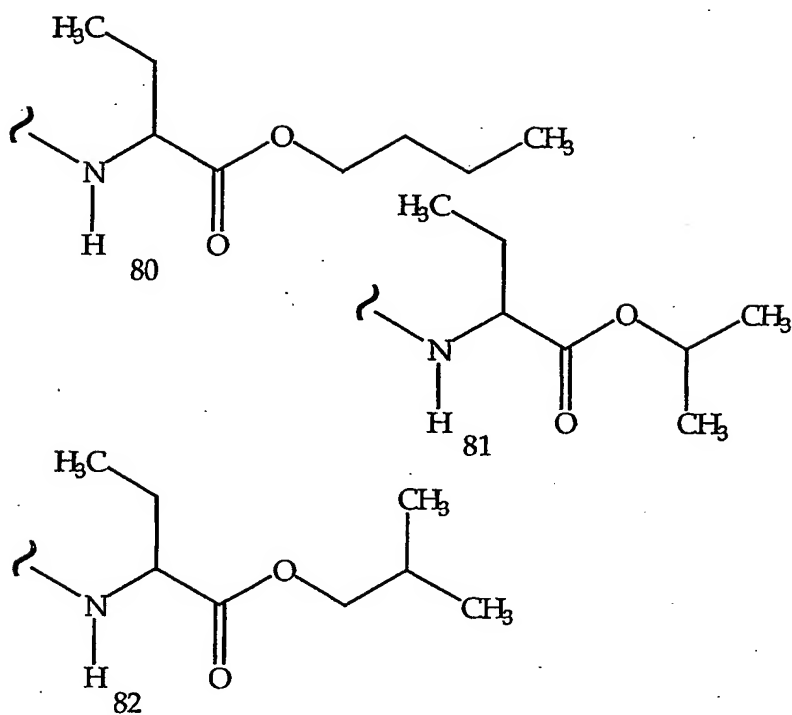
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Table 20.15

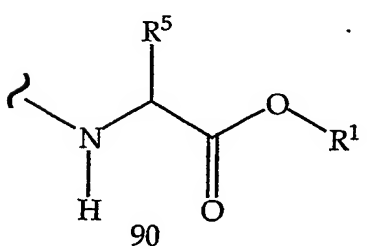
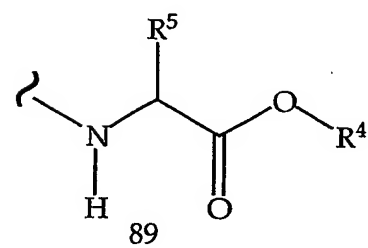
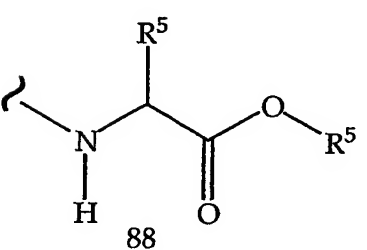
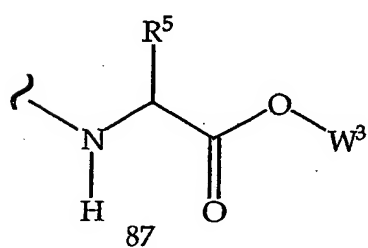
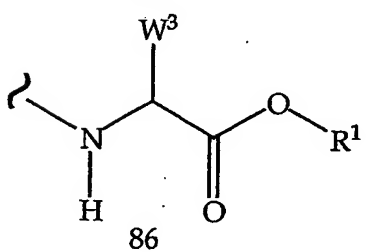
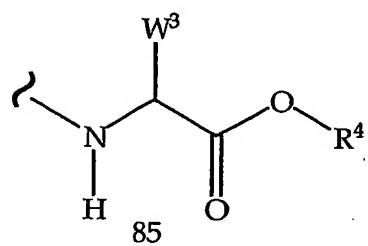
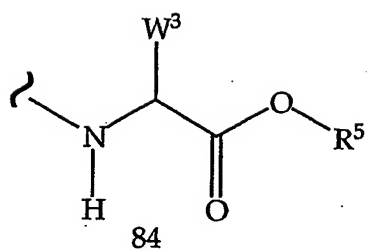
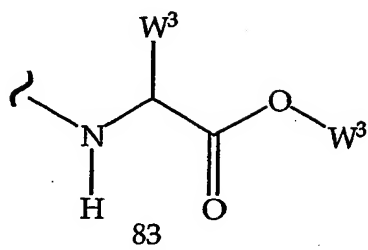


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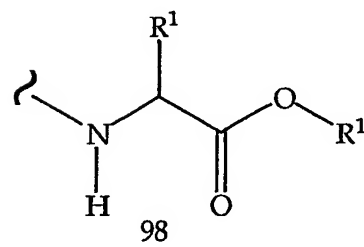
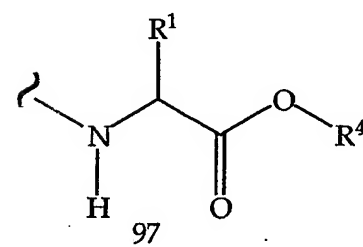
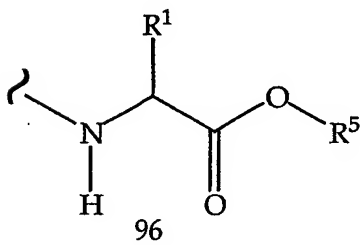
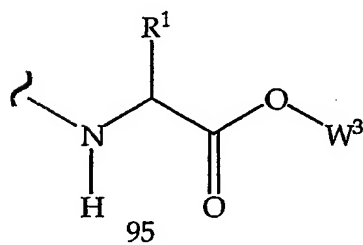
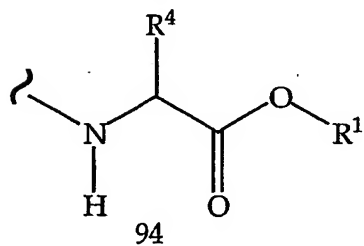
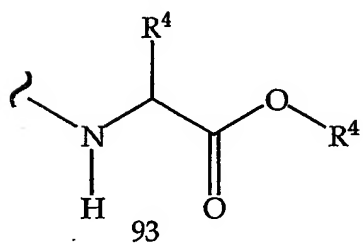
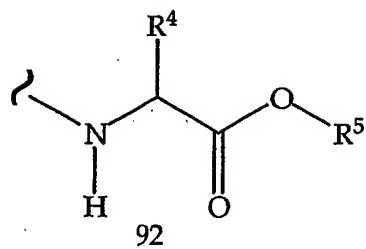
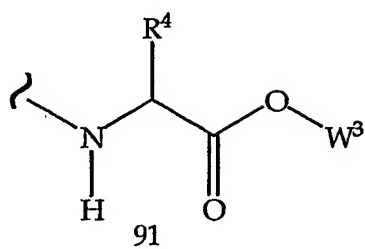


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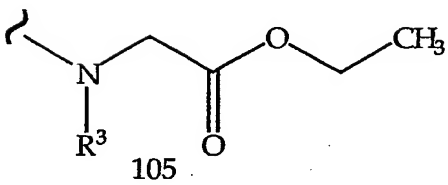
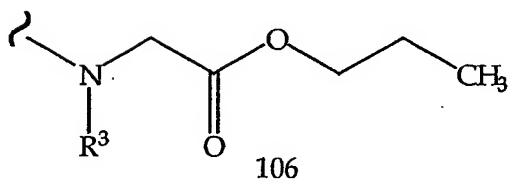
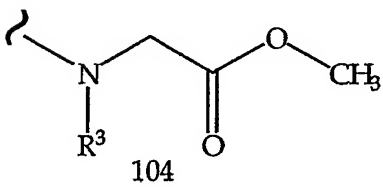
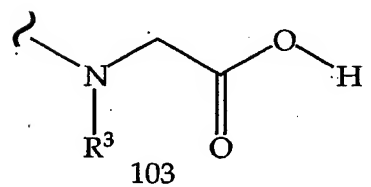
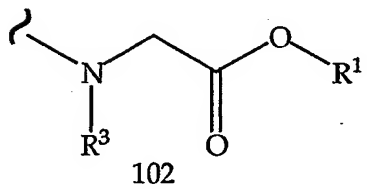
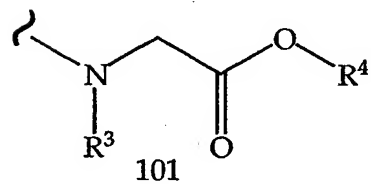
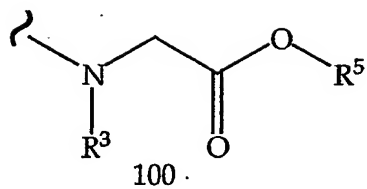
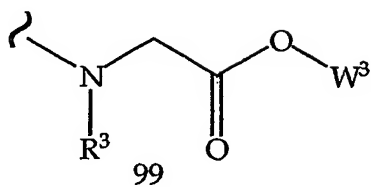


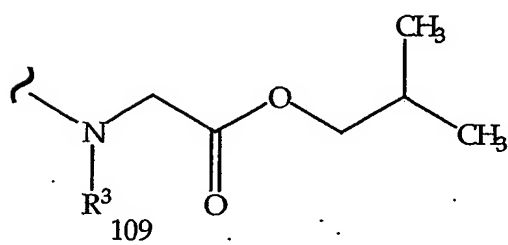
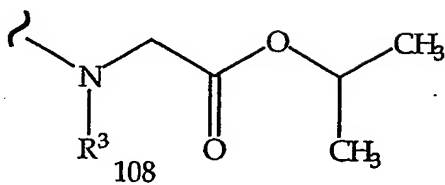
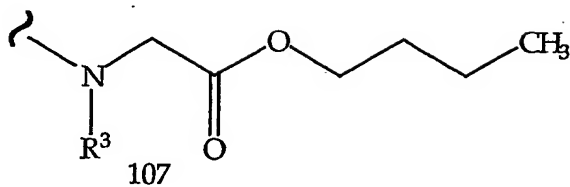
Table 20.18

Table 20.19

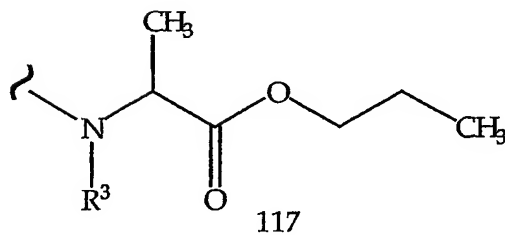
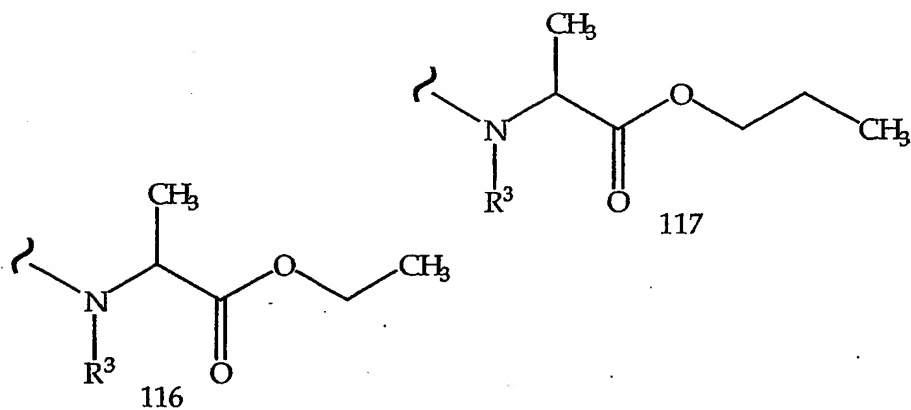
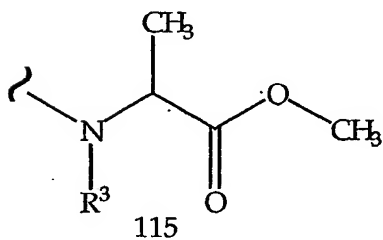
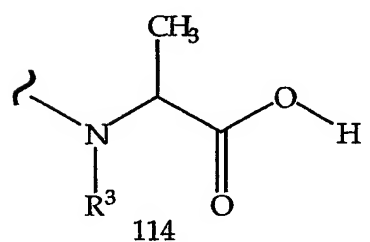
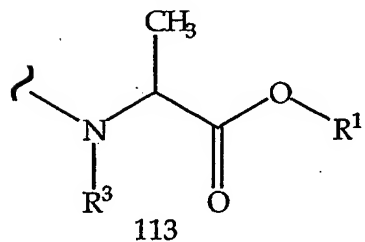
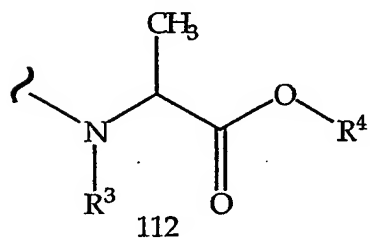
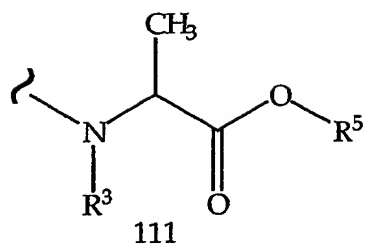
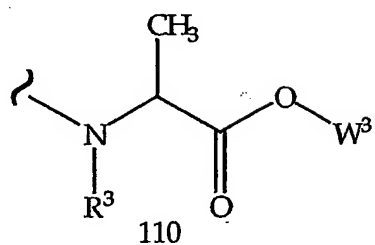


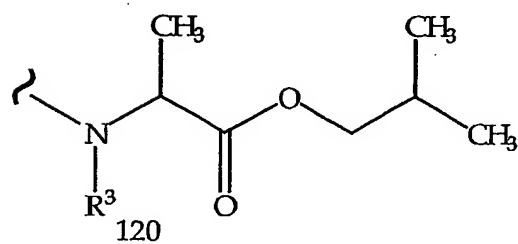
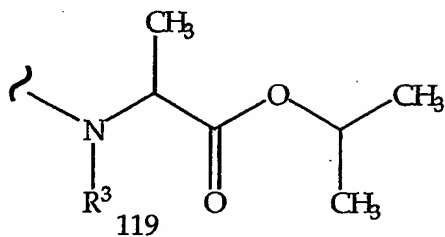
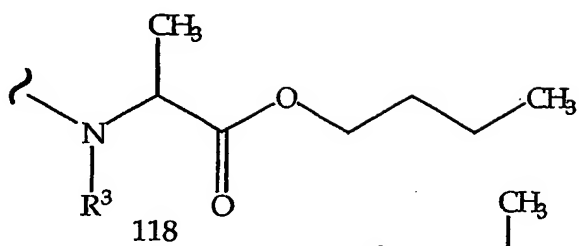
Table 20.20

Table 20.21

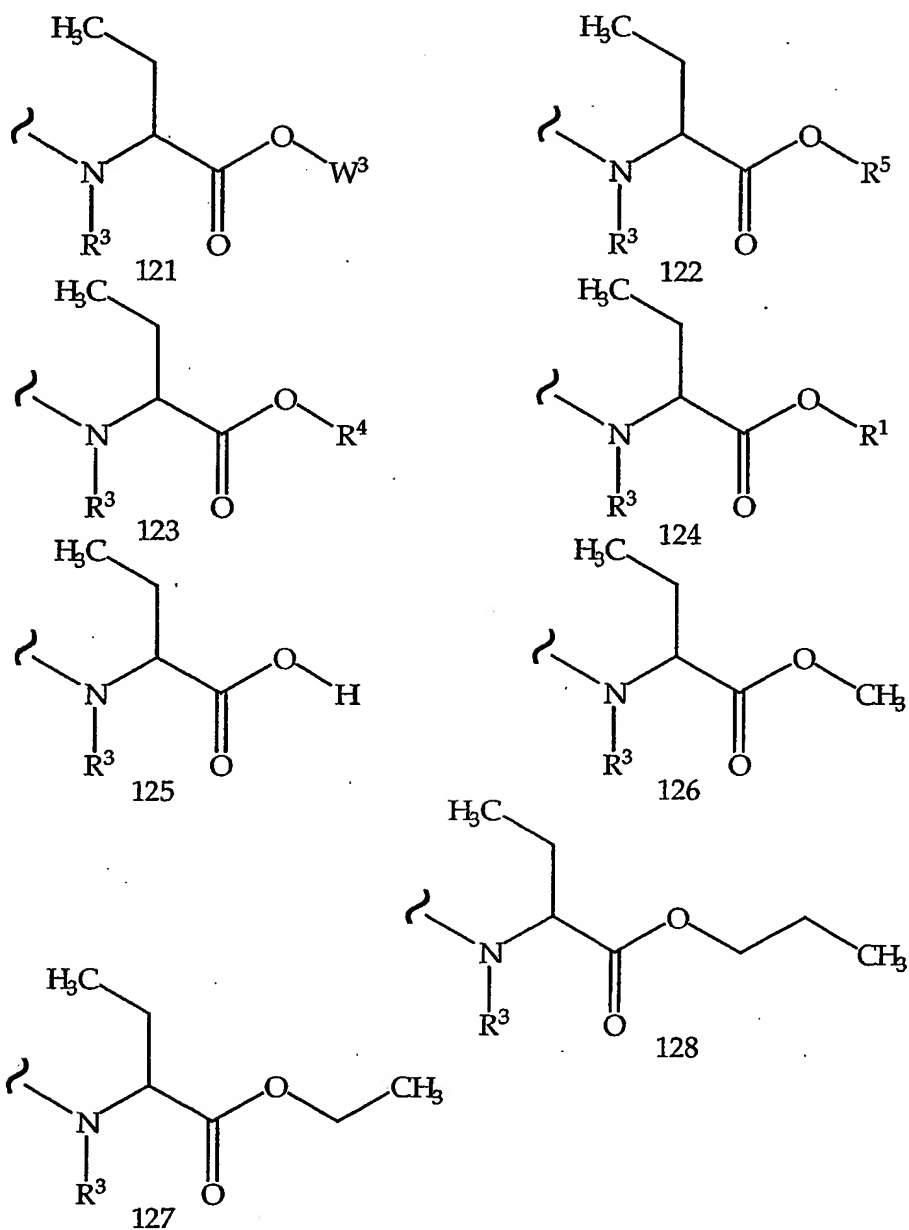


Table 20.22

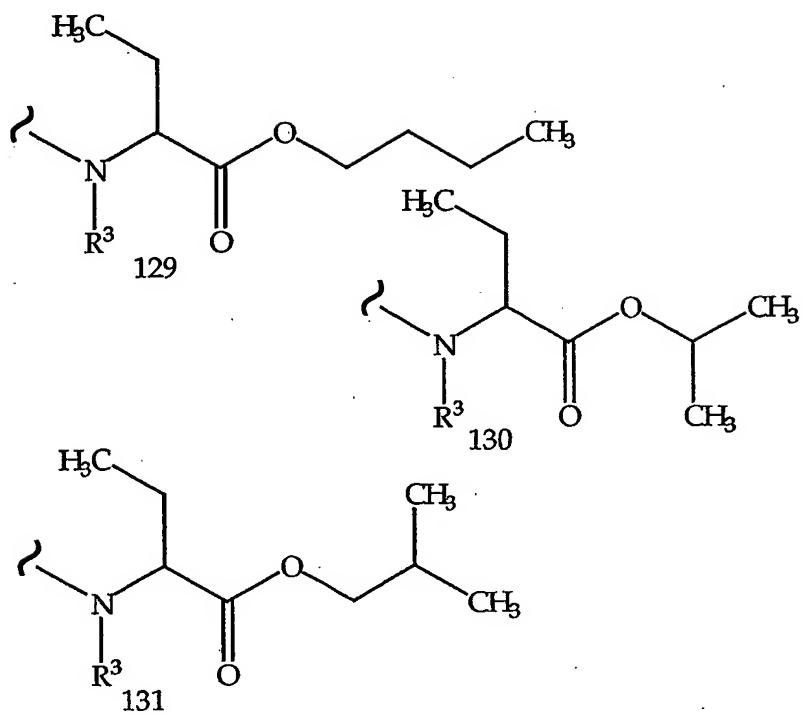


Table 20.23

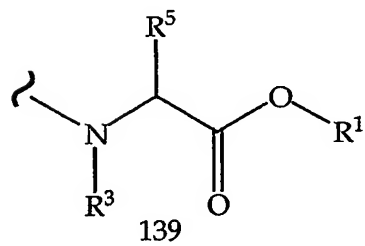
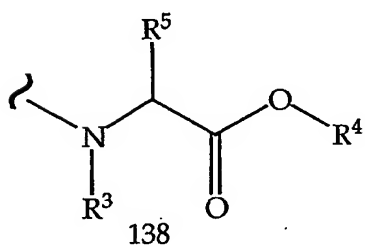
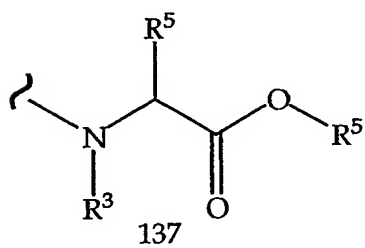
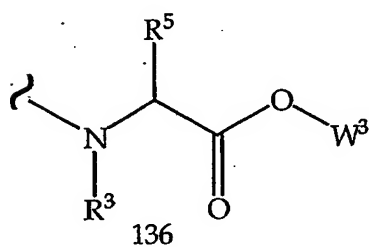
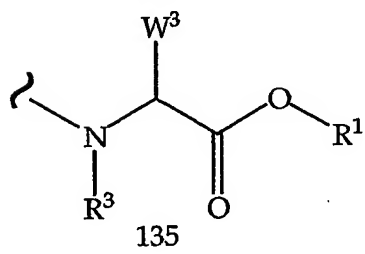
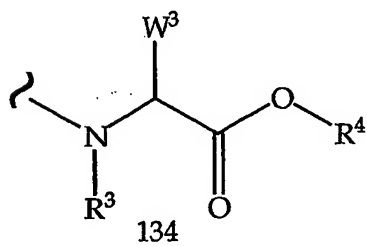
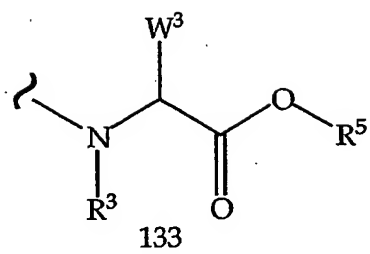
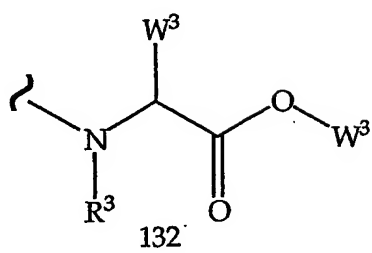


Table 20.24

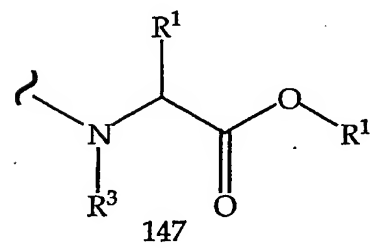
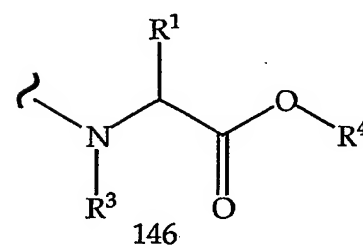
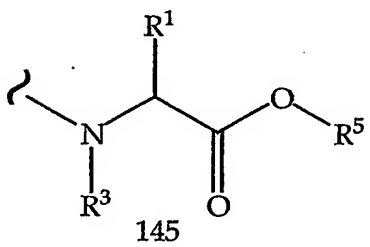
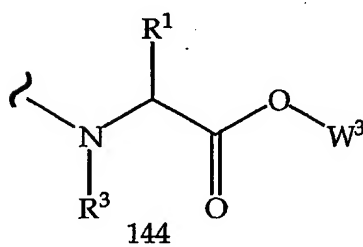
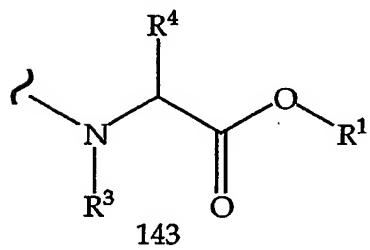
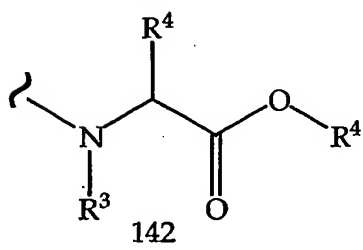
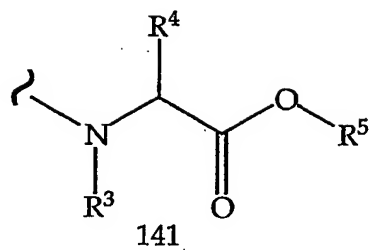
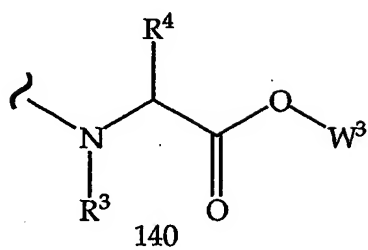
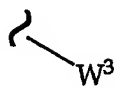
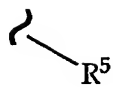
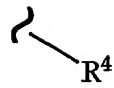


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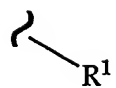
148



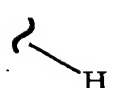
149



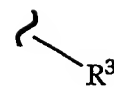
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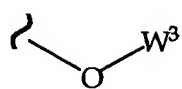
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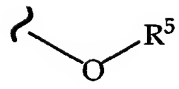
152



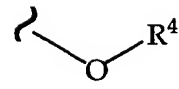
153



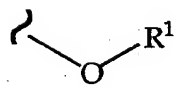
154



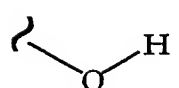
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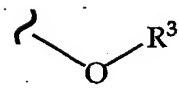
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157

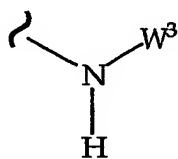


158

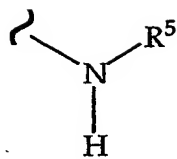


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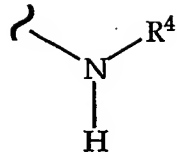
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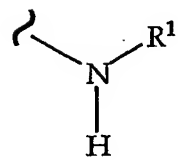
160



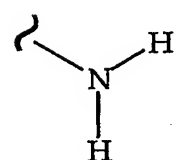
161



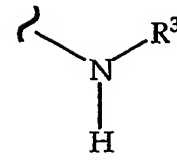
162



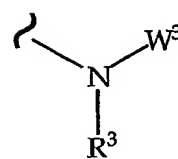
163



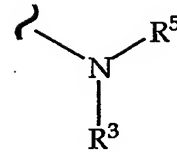
164



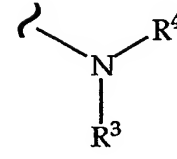
165



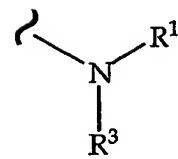
166



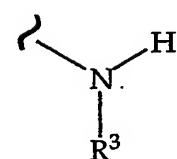
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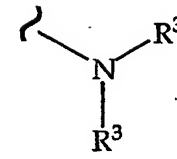
168



169

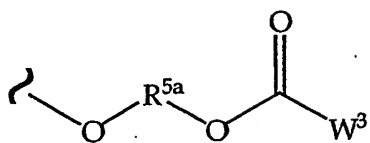


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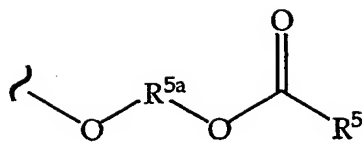


171

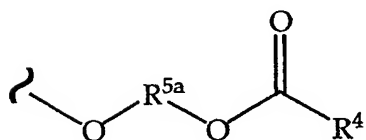
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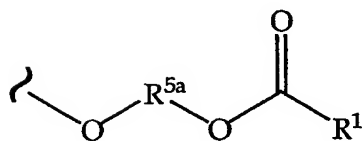
172



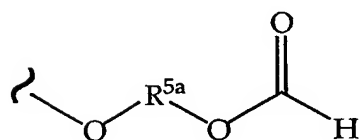
173



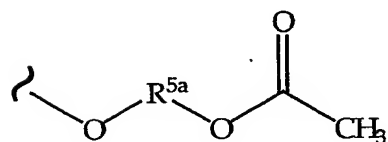
174



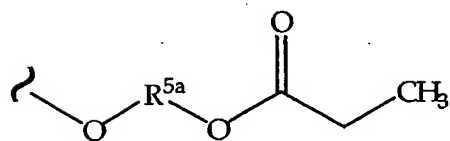
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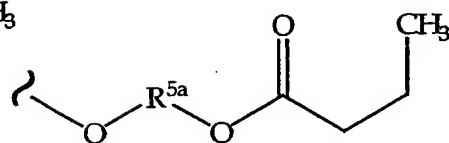
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177

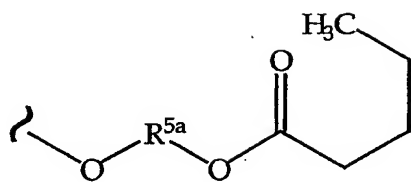


178

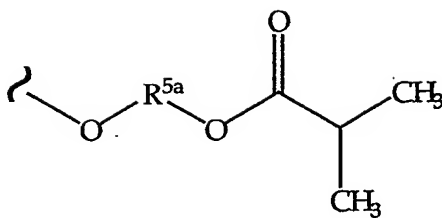


179

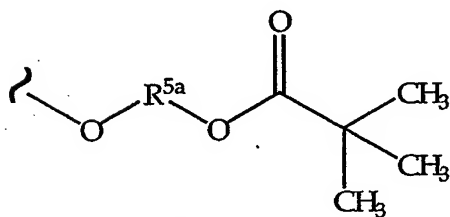
Table 20.28



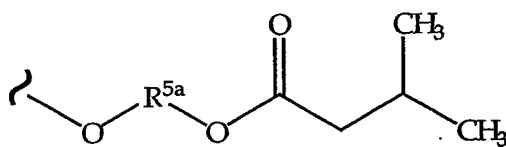
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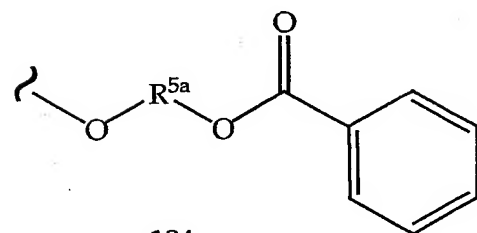
181



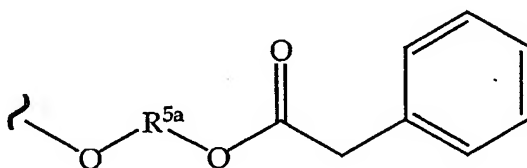
182



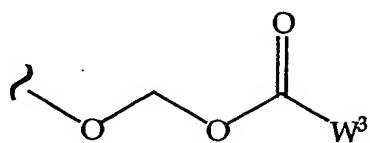
183



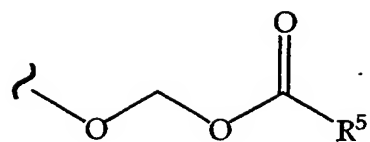
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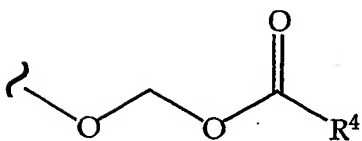
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Table 20.29

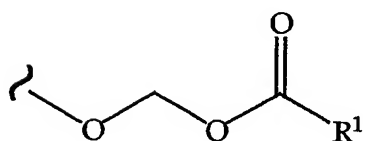
186



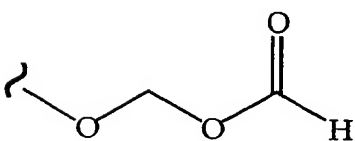
187



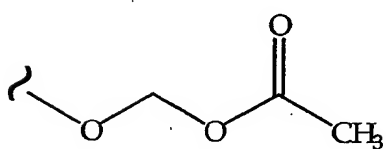
188



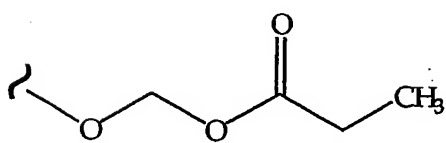
189



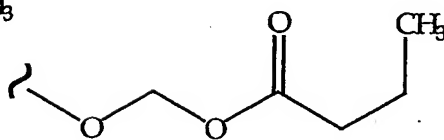
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191

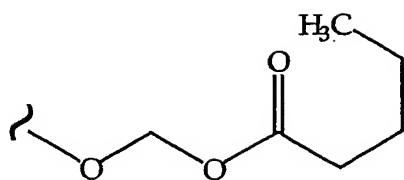


192

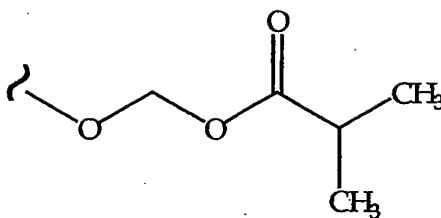


193

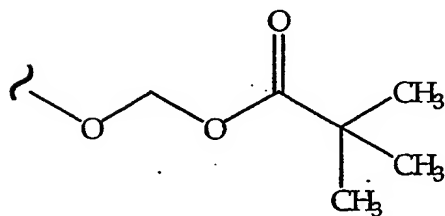
Table 20.30



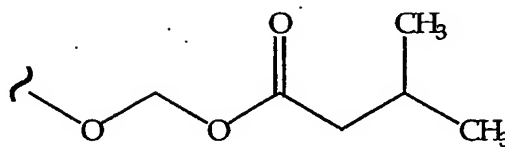
194



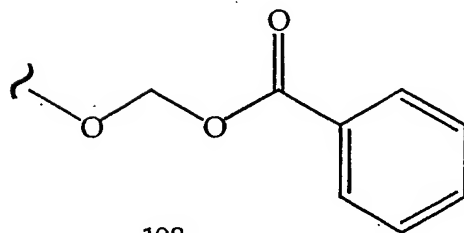
195



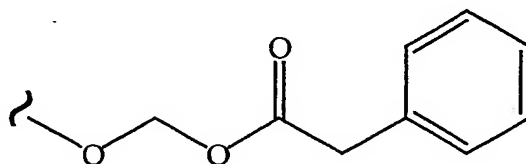
196



197

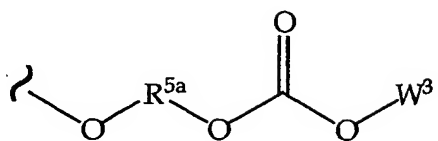


198

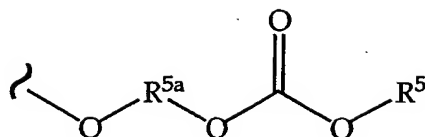


199

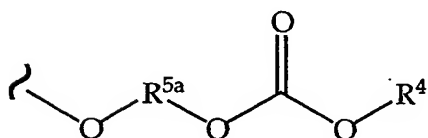
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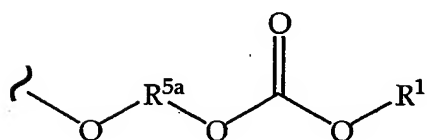
200



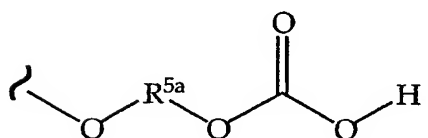
201



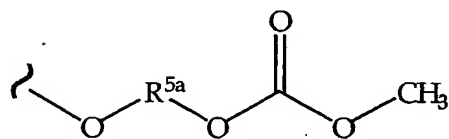
202



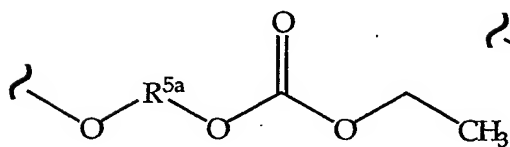
203



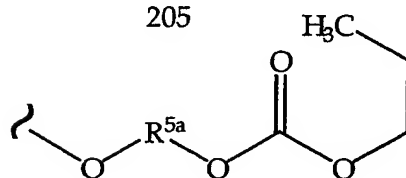
204



205

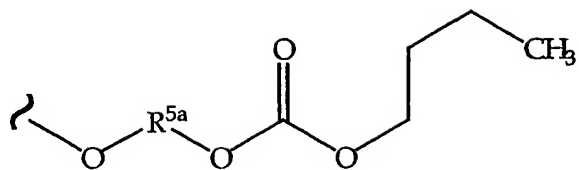


206

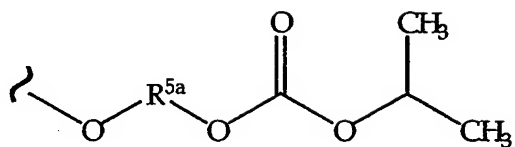


207

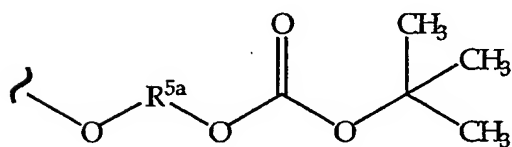
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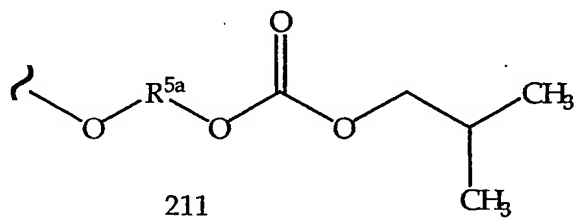
208



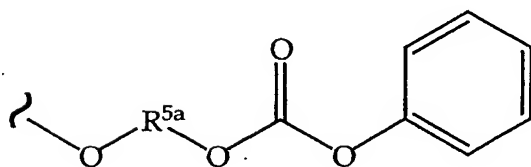
209



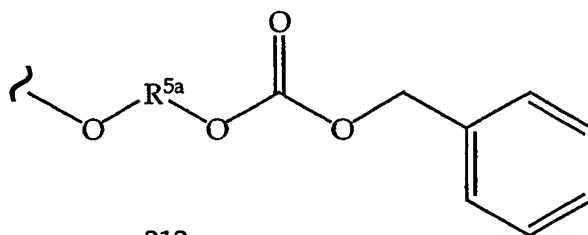
210



211

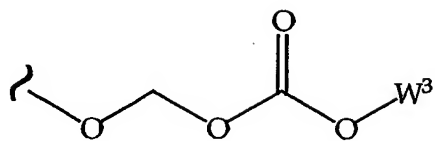


212

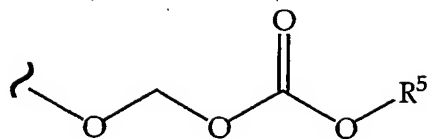


213

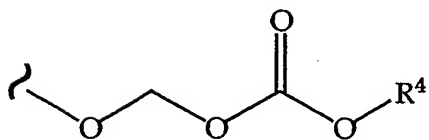
Table 20.33



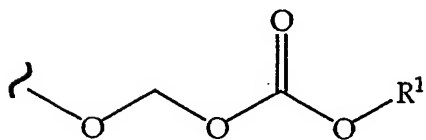
214.



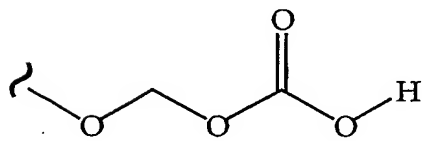
215



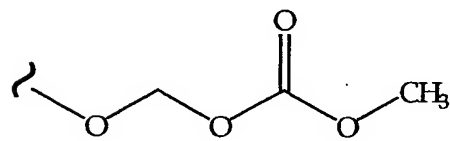
216



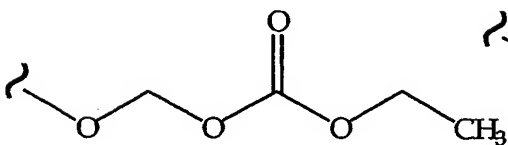
217



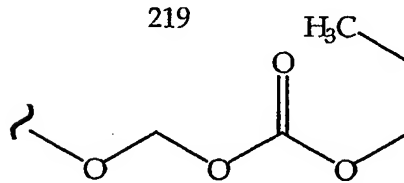
218



219

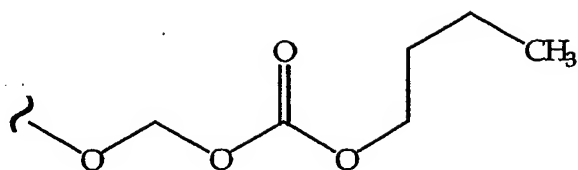


220

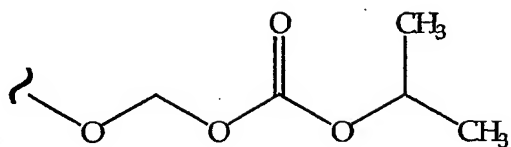


221

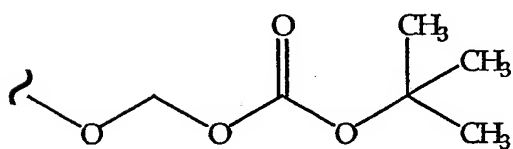
Table 20.34



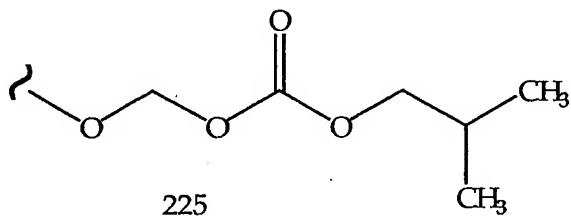
222



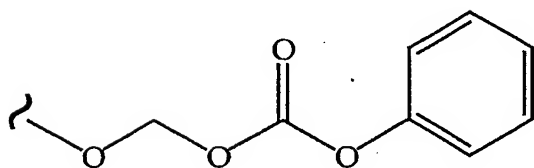
223



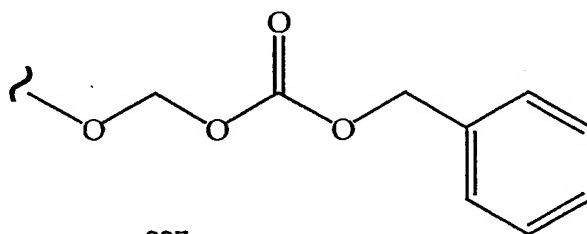
224



225



226



227

Table 20.35

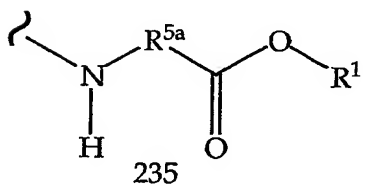
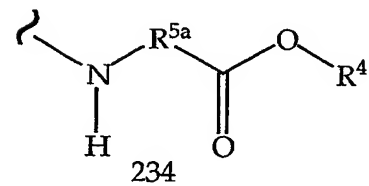
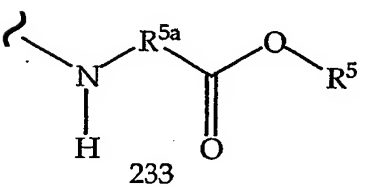
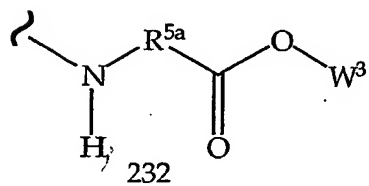
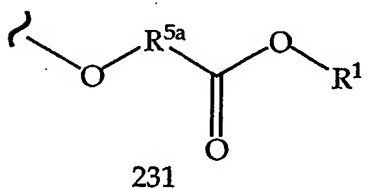
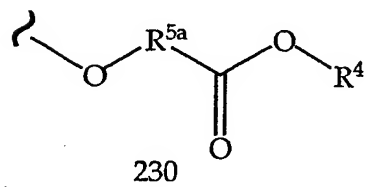
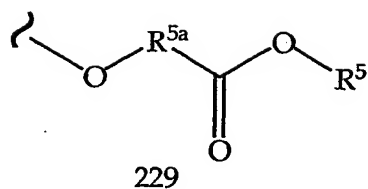
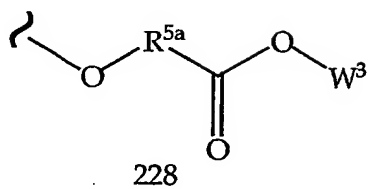


Table 20.36

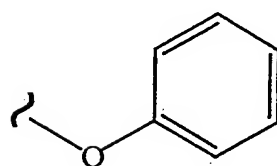
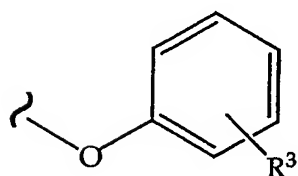
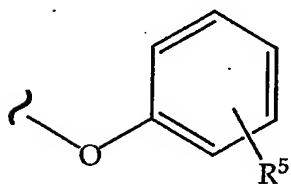
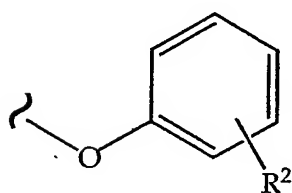
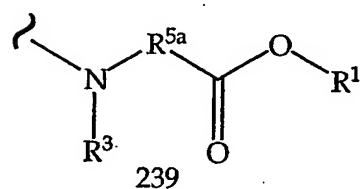
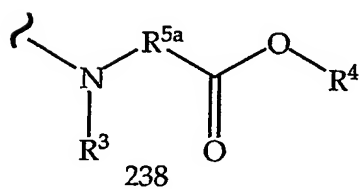
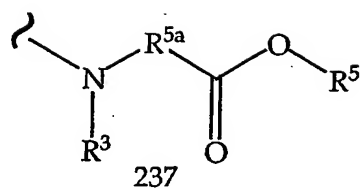
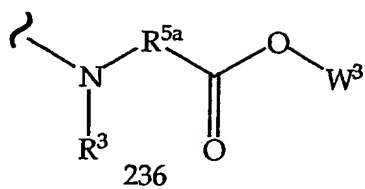


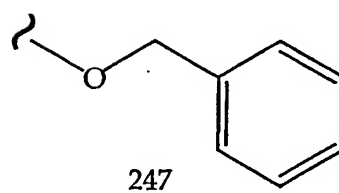
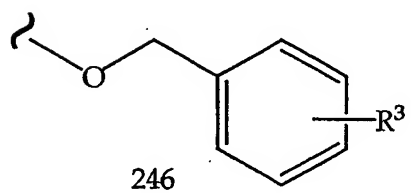
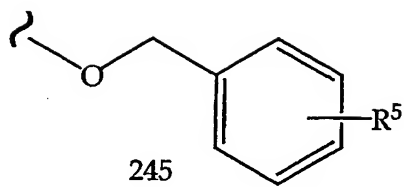
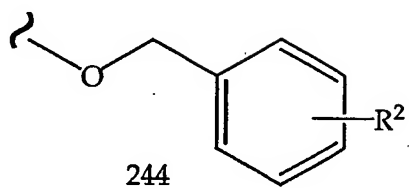
Table 20.37

Table 100

Prodrugs of 1.B

- 1.B.228.228; 1.B.228.229; 1.B.228.230; 1.B.228.231; 1.B.228.236; 1.B.228.237;
- 5 1.B.228.238; 1.B.228.239; 1.B.228.154; 1.B.228.157; 1.B.228.166; 1.B.228.169; 1.B.228.172;
1.B.228.175; 1.B.228.240; 1.B.228.244; 1.B.229.228; 1.B.229.229; 1.B.229.230; 1.B.229.231;
1.B.229.236; 1.B.229.237; 1.B.229.238; 1.B.229.239; 1.B.229.154; 1.B.229.157; 1.B.229.166;
1.B.229.169; 1.B.229.172; 1.B.229.175; 1.B.229.240; 1.B.229.244; 1.B.230.228; 1.B.230.229;
1.B.230.230; 1.B.230.231; 1.B.230.236; 1.B.230.237; 1.B.230.238; 1.B.230.239; 1.B.230.154;
- 10 1.B.230.157; 1.B.230.166; 1.B.230.169; 1.B.230.172; 1.B.230.175; 1.B.230.240; 1.B.230.244;
1.B.231.228; 1.B.231.229; 1.B.231.230; 1.B.231.231; 1.B.231.236; 1.B.231.237; 1.B.231.238;
1.B.231.239; 1.B.231.154; 1.B.231.157; 1.B.231.166; 1.B.231.169; 1.B.231.172; 1.B.231.175;
1.B.231.240; 1.B.231.244; 1.B.236.228; 1.B.236.229; 1.B.236.230; 1.B.236.231; 1.B.236.236;
1.B.236.237; 1.B.236.238; 1.B.236.239; 1.B.236.154; 1.B.236.157; 1.B.236.166; 1.B.236.169;
- 15 1.B.236.172; 1.B.236.175; 1.B.236.240; 1.B.236.244; 1.B.237.228; 1.B.237.229; 1.B.237.230;
1.B.237.231; 1.B.237.236; 1.B.237.237; 1.B.237.238; 1.B.237.239; 1.B.237.154; 1.B.237.157;
1.B.237.166; 1.B.237.169; 1.B.237.172; 1.B.237.175; 1.B.237.240; 1.B.237.244; 1.B.238.228;
1.B.238.229; 1.B.238.230; 1.B.238.231; 1.B.238.236; 1.B.238.237; 1.B.238.238; 1.B.238.239;
1.B.238.154; 1.B.238.157; 1.B.238.166; 1.B.238.169; 1.B.238.172; 1.B.238.175; 1.B.238.240;
- 20 1.B.238.244; 1.B.239.228; 1.B.239.229; 1.B.239.230; 1.B.239.231; 1.B.239.236; 1.B.239.237;
1.B.239.238; 1.B.239.239; 1.B.239.154; 1.B.239.157; 1.B.239.166; 1.B.239.169; 1.B.239.172;
1.B.239.175; 1.B.239.240; 1.B.239.244; 1.B.154.228; 1.B.154.229; 1.B.154.230; 1.B.154.231;
1.B.154.236; 1.B.154.237; 1.B.154.238; 1.B.154.239; 1.B.154.154; 1.B.154.157; 1.B.154.166;
1.B.154.169; 1.B.154.172; 1.B.154.175; 1.B.154.240; 1.B.154.244; 1.B.157.228; 1.B.157.229;
- 25 1.B.157.230; 1.B.157.231; 1.B.157.236; 1.B.157.237; 1.B.157.238; 1.B.157.239; 1.B.157.154;
1.B.157.157; 1.B.157.166; 1.B.157.169; 1.B.157.172; 1.B.157.175; 1.B.157.240; 1.B.157.244;
1.B.166.228; 1.B.166.229; 1.B.166.230; 1.B.166.231; 1.B.166.236; 1.B.166.237; 1.B.166.238;
1.B.166.239; 1.B.166.154; 1.B.166.157; 1.B.166.166; 1.B.166.169; 1.B.166.172; 1.B.166.175;
1.B.166.240; 1.B.166.244; 1.B.169.228; 1.B.169.229; 1.B.169.230; 1.B.169.231; 1.B.169.236;
- 30 1.B.169.237; 1.B.169.238; 1.B.169.239; 1.B.169.154; 1.B.169.157; 1.B.169.166; 1.B.169.169;
1.B.169.172; 1.B.169.175; 1.B.169.240; 1.B.169.244; 1.B.172.228; 1.B.172.229; 1.B.172.230;
1.B.172.231; 1.B.172.236; 1.B.172.237; 1.B.172.238; 1.B.172.239; 1.B.172.154; 1.B.172.157;
1.B.172.166; 1.B.172.169; 1.B.172.172; 1.B.172.175; 1.B.172.240; 1.B.172.244; 1.B.175.228;
1.B.175.229; 1.B.175.230; 1.B.175.231; 1.B.175.236; 1.B.175.237; 1.B.175.238; 1.B.175.239;
- 35 1.B.175.154; 1.B.175.157; 1.B.175.166; 1.B.175.169; 1.B.175.172; 1.B.175.175; 1.B.175.240;
1.B.175.244; 1.B.240.228; 1.B.240.229; 1.B.240.230; 1.B.240.231; 1.B.240.236; 1.B.240.237;
1.B.240.238; 1.B.240.239; 1.B.240.154; 1.B.240.157; 1.B.240.166; 1.B.240.169; 1.B.240.172;
1.B.240.175; 1.B.240.240; 1.B.240.244; 1.B.244.228; 1.B.244.229; 1.B.244.230; 1.B.244.231;
1.B.244.236; 1.B.244.237; 1.B.244.238; 1.B.244.239; 1.B.244.154; 1.B.244.157; 1.B.244.166;
- 40 1.B.244.169; 1.B.244.172; 1.B.244.175; 1.B.244.240; 1.B.244.244;

Prodrugs of 1.D

- 1.D.228.228; 1.D.228.229; 1.D.228.230; 1.D.228.231; 1.D.228.236; 1.D.228.237;
1.D.228.238; 1.D.228.239; 1.D.228.154; 1.D.228.157; 1.D.228.166; 1.D.228.169;
- 45 1.D.228.172; 1.D.228.175; 1.D.228.240; 1.D.228.244; 1.D.229.228; 1.D.229.229;
1.D.229.230; 1.D.229.231; 1.D.229.236; 1.D.229.237; 1.D.229.238; 1.D.229.239;

- 1.D.229.154; 1.D.229.157; 1.D.229.166; 1.D.229.169; 1.D.229.172; 1.D.229.175;
 1.D.229.240; 1.D.229.244; 1.D.230.228; 1.D.230.229; 1.D.230.230; 1.D.230.231;
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 1.D.230.166; 1.D.230.169; 1.D.230.172; 1.D.230.175; 1.D.230.240; 1.D.230.244;
 5 1.D.231.228; 1.D.231.229; 1.D.231.230; 1.D.231.231; 1.D.231.236; 1.D.231.237;
 1.D.231.238; 1.D.231.239; 1.D.231.154; 1.D.231.157; 1.D.231.166; 1.D.231.169;
 1.D.231.172; 1.D.231.175; 1.D.231.240; 1.D.231.244; 1.D.236.228; 1.D.236.229;
 1.D.236.230; 1.D.236.231; 1.D.236.236; 1.D.236.237; 1.D.236.238; 1.D.236.239;
 1.D.236.154; 1.D.236.157; 1.D.236.166; 1.D.236.169; 1.D.236.172; 1.D.236.175;
 10 1.D.236.240; 1.D.236.244; 1.D.237.228; 1.D.237.229; 1.D.237.230; 1.D.237.231;
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 1.D.238.238; 1.D.238.239; 1.D.238.154; 1.D.238.157; 1.D.238.166; 1.D.238.169;
 15 1.D.238.172; 1.D.238.175; 1.D.238.240; 1.D.238.244; 1.D.239.228; 1.D.239.229;
 1.D.239.230; 1.D.239.231; 1.D.239.236; 1.D.239.237; 1.D.239.238; 1.D.239.239;
 1.D.239.154; 1.D.239.157; 1.D.239.166; 1.D.239.169; 1.D.239.172; 1.D.239.175;
 1.D.239.240; 1.D.239.244; 1.D.154.228; 1.D.154.229; 1.D.154.230; 1.D.154.231;
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 20 1.D.154.166; 1.D.154.169; 1.D.154.172; 1.D.154.175; 1.D.154.240; 1.D.154.244;
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 1.D.166.230; 1.D.166.231; 1.D.166.236; 1.D.166.237; 1.D.166.238; 1.D.166.239;
 25 1.D.166.154; 1.D.166.157; 1.D.166.166; 1.D.166.169; 1.D.166.172; 1.D.166.175;
 1.D.166.240; 1.D.166.244; 1.D.169.228; 1.D.169.229; 1.D.169.230; 1.D.169.231;
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 35 1.D.240.236; 1.D.240.237; 1.D.240.238; 1.D.240.239; 1.D.240.154; 1.D.240.157;
 1.D.240.166; 1.D.240.169; 1.D.240.172; 1.D.240.175; 1.D.240.240; 1.D.240.244;
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 1.D.244.238; 1.D.244.239; 1.D.244.154; 1.D.244.157; 1.D.244.166; 1.D.244.169;
 1.D.244.172; 1.D.244.175; 1.D.244.240; 1.D.244.244;

40

Prodrugs of 1.E

- 1.E.228.228; 1.E.228.229; 1.E.228.230; 1.E.228.231; 1.E.228.236; 1.E.228.237;
 1.E.228.238; 1.E.228.239; 1.E.228.154; 1.E.228.157; 1.E.228.166; 1.E.228.169; 1.E.228.172;
 1.E.228.175; 1.E.228.240; 1.E.228.244; 1.E.229.228; 1.E.229.229; 1.E.229.230; 1.E.229.231;
 45 1.E.229.236; 1.E.229.237; 1.E.229.238; 1.E.229.239; 1.E.229.154; 1.E.229.157; 1.E.229.166;
 1.E.229.169; 1.E.229.172; 1.E.229.175; 1.E.229.240; 1.E.229.244; 1.E.230.228; 1.E.230.229;

- 1.E.230.230; 1.E.230.231; 1.E.230.236; 1.E.230.237; 1.E.230.238; 1.E.230.239; 1.E.230.154;
 1.E.230.157; 1.E.230.166; 1.E.230.169; 1.E.230.172; 1.E.230.175; 1.E.230.240; 1.E.230.244;
 1.E.231.228; 1.E.231.229; 1.E.231.230; 1.E.231.231; 1.E.231.236; 1.E.231.237; 1.E.231.238;
 1.E.231.239; 1.E.231.154; 1.E.231.157; 1.E.231.166; 1.E.231.169; 1.E.231.172; 1.E.231.175;
 5 1.E.231.240; 1.E.231.244; 1.E.236.228; 1.E.236.229; 1.E.236.230; 1.E.236.231; 1.E.236.236;
 1.E.236.237; 1.E.236.238; 1.E.236.239; 1.E.236.154; 1.E.236.157; 1.E.236.166; 1.E.236.169;
 1.E.236.172; 1.E.236.175; 1.E.236.240; 1.E.236.244; 1.E.237.228; 1.E.237.229; 1.E.237.230;
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 1.E.237.166; 1.E.237.169; 1.E.237.172; 1.E.237.175; 1.E.237.240; 1.E.237.244; 1.E.238.228;
 10 1.E.238.229; 1.E.238.230; 1.E.238.231; 1.E.238.236; 1.E.238.237; 1.E.238.238; 1.E.238.239;
 1.E.238.154; 1.E.238.157; 1.E.238.166; 1.E.238.169; 1.E.238.172; 1.E.238.175; 1.E.238.240;
 1.E.238.244; 1.E.239.228; 1.E.239.229; 1.E.239.230; 1.E.239.231; 1.E.239.236; 1.E.239.237;
 1.E.239.238; 1.E.239.239; 1.E.239.154; 1.E.239.157; 1.E.239.166; 1.E.239.169; 1.E.239.172;
 1.E.239.175; 1.E.239.240; 1.E.239.244; 1.E.154.228; 1.E.154.229; 1.E.154.230; 1.E.154.231;
 15 1.E.154.236; 1.E.154.237; 1.E.154.238; 1.E.154.239; 1.E.154.154; 1.E.154.157; 1.E.154.166;
 1.E.154.169; 1.E.154.172; 1.E.154.175; 1.E.154.240; 1.E.154.244; 1.E.157.228; 1.E.157.229;
 1.E.157.230; 1.E.157.231; 1.E.157.236; 1.E.157.237; 1.E.157.238; 1.E.157.239; 1.E.157.154;
 1.E.157.157; 1.E.157.166; 1.E.157.169; 1.E.157.172; 1.E.157.175; 1.E.157.240; 1.E.157.244;
 1.E.166.228; 1.E.166.229; 1.E.166.230; 1.E.166.231; 1.E.166.236; 1.E.166.237; 1.E.166.238;
 20 1.E.166.239; 1.E.166.154; 1.E.166.157; 1.E.166.166; 1.E.166.169; 1.E.166.172; 1.E.166.175;
 1.E.166.240; 1.E.166.244; 1.E.169.228; 1.E.169.229; 1.E.169.230; 1.E.169.231; 1.E.169.236;
 1.E.169.237; 1.E.169.238; 1.E.169.239; 1.E.169.154; 1.E.169.157; 1.E.169.166; 1.E.169.169;
 1.E.169.172; 1.E.169.175; 1.E.169.240; 1.E.169.244; 1.E.172.228; 1.E.172.229; 1.E.172.230;
 1.E.172.231; 1.E.172.236; 1.E.172.237; 1.E.172.238; 1.E.172.239; 1.E.172.154; 1.E.172.157;
 25 1.E.172.166; 1.E.172.169; 1.E.172.172; 1.E.172.175; 1.E.172.240; 1.E.172.244; 1.E.175.228;
 1.E.175.229; 1.E.175.230; 1.E.175.231; 1.E.175.236; 1.E.175.237; 1.E.175.238; 1.E.175.239;
 1.E.175.154; 1.E.175.157; 1.E.175.166; 1.E.175.169; 1.E.175.172; 1.E.175.175; 1.E.175.240;
 1.E.175.244; 1.E.240.228; 1.E.240.229; 1.E.240.230; 1.E.240.231; 1.E.240.236; 1.E.240.237;
 1.E.240.238; 1.E.240.239; 1.E.240.154; 1.E.240.157; 1.E.240.166; 1.E.240.169; 1.E.240.172;
 30 1.E.240.175; 1.E.240.240; 1.E.240.244; 1.E.244.228; 1.E.244.229; 1.E.244.230; 1.E.244.231;
 1.E.244.236; 1.E.244.237; 1.E.244.238; 1.E.244.239; 1.E.244.154; 1.E.244.157; 1.E.244.166;
 1.E.244.169; 1.E.244.172; 1.E.244.175; 1.E.244.240; 1.E.244.244;

Prodrugs of 1.G

- 35 1.G.228.228; 1.G.228.229; 1.G.228.230; 1.G.228.231; 1.G.228.236; 1.G.228.237;
 1.G.228.238; 1.G.228.239; 1.G.228.154; 1.G.228.157; 1.G.228.166; 1.G.228.169;
 1.G.228.172; 1.G.228.175; 1.G.228.240; 1.G.228.244; 1.G.229.228; 1.G.229.229;
 1.G.229.230; 1.G.229.231; 1.G.229.236; 1.G.229.237; 1.G.229.238; 1.G.229.239;
 1.G.229.154; 1.G.229.157; 1.G.229.166; 1.G.229.169; 1.G.229.172; 1.G.229.175;
 40 1.G.229.240; 1.G.229.244; 1.G.230.228; 1.G.230.229; 1.G.230.230; 1.G.230.231;
 1.G.230.236; 1.G.230.237; 1.G.230.238; 1.G.230.239; 1.G.230.154; 1.G.230.157;
 1.G.230.166; 1.G.230.169; 1.G.230.172; 1.G.230.175; 1.G.230.240; 1.G.230.244;
 1.G.231.228; 1.G.231.229; 1.G.231.230; 1.G.231.231; 1.G.231.236; 1.G.231.237;
 1.G.231.238; 1.G.231.239; 1.G.231.154; 1.G.231.157; 1.G.231.166; 1.G.231.169;
 45 1.G.231.172; 1.G.231.175; 1.G.231.240; 1.G.231.244; 1.G.236.228; 1.G.236.229;
 1.G.236.230; 1.G.236.231; 1.G.236.236; 1.G.236.237; 1.G.236.238; 1.G.236.239;

- 1.G.236.154; 1.G.236.157; 1.G.236.166; 1.G.236.169; 1.G.236.172; 1.G.236.175;
 1.G.236.240; 1.G.236.244; 1.G.237.228; 1.G.237.229; 1.G.237.230; 1.G.237.231;
 1.G.237.236; 1.G.237.237; 1.G.237.238; 1.G.237.239; 1.G.237.154; 1.G.237.157;
 1.G.237.166; 1.G.237.169; 1.G.237.172; 1.G.237.175; 1.G.237.240; 1.G.237.244;
 5 1.G.238.228; 1.G.238.229; 1.G.238.230; 1.G.238.231; 1.G.238.236; 1.G.238.237;
 1.G.238.238; 1.G.238.239; 1.G.238.154; 1.G.238.157; 1.G.238.166; 1.G.238.169;
 1.G.238.172; 1.G.238.175; 1.G.238.240; 1.G.238.244; 1.G.239.228; 1.G.239.229;
 1.G.239.230; 1.G.239.231; 1.G.239.236; 1.G.239.237; 1.G.239.238; 1.G.239.239;
 1.G.239.154; 1.G.239.157; 1.G.239.166; 1.G.239.169; 1.G.239.172; 1.G.239.175;
 10 1.G.239.240; 1.G.239.244; 1.G.154.228; 1.G.154.229; 1.G.154.230; 1.G.154.231;
 1.G.154.236; 1.G.154.237; 1.G.154.238; 1.G.154.239; 1.G.154.154; 1.G.154.157;
 1.G.154.166; 1.G.154.169; 1.G.154.172; 1.G.154.175; 1.G.154.240; 1.G.154.244;
 1.G.157.228; 1.G.157.229; 1.G.157.230; 1.G.157.231; 1.G.157.236; 1.G.157.237;
 1.G.157.238; 1.G.157.239; 1.G.157.154; 1.G.157.157; 1.G.157.166; 1.G.157.169;
 15 1.G.157.172; 1.G.157.175; 1.G.157.240; 1.G.157.244; 1.G.166.228; 1.G.166.229;
 1.G.166.230; 1.G.166.231; 1.G.166.236; 1.G.166.237; 1.G.166.238; 1.G.166.239;
 1.G.166.154; 1.G.166.157; 1.G.166.166; 1.G.166.169; 1.G.166.172; 1.G.166.175;
 1.G.166.240; 1.G.166.244; 1.G.169.228; 1.G.169.229; 1.G.169.230; 1.G.169.231;
 1.G.169.236; 1.G.169.237; 1.G.169.238; 1.G.169.239; 1.G.169.154; 1.G.169.157;
 20 1.G.169.166; 1.G.169.169; 1.G.169.172; 1.G.169.175; 1.G.169.240; 1.G.169.244;
 1.G.172.228; 1.G.172.229; 1.G.172.230; 1.G.172.231; 1.G.172.236; 1.G.172.237;
 1.G.172.238; 1.G.172.239; 1.G.172.154; 1.G.172.157; 1.G.172.166; 1.G.172.169;
 1.G.172.172; 1.G.172.175; 1.G.172.240; 1.G.172.244; 1.G.175.228; 1.G.175.229;
 1.G.175.230; 1.G.175.231; 1.G.175.236; 1.G.175.237; 1.G.175.238; 1.G.175.239;
 25 1.G.175.154; 1.G.175.157; 1.G.175.166; 1.G.175.169; 1.G.175.172; 1.G.175.175;
 1.G.175.240; 1.G.175.244; 1.G.240.228; 1.G.240.229; 1.G.240.230; 1.G.240.231;
 1.G.240.236; 1.G.240.237; 1.G.240.238; 1.G.240.239; 1.G.240.154; 1.G.240.157;
 1.G.240.166; 1.G.240.169; 1.G.240.172; 1.G.240.175; 1.G.240.240; 1.G.240.244;
 1.G.244.228; 1.G.244.229; 1.G.244.230; 1.G.244.231; 1.G.244.236; 1.G.244.237;
 30 1.G.244.238; 1.G.244.239; 1.G.244.154; 1.G.244.157; 1.G.244.166; 1.G.244.169;
 1.G.244.172; 1.G.244.175; 1.G.244.240; 1.G.244.244;

Prodrugs of 1.I

- 1.I.228.228; 1.I.228.229; 1.I.228.230; 1.I.228.231; 1.I.228.236; 1.I.228.237; 1.I.228.238;
 35 1.I.228.239; 1.I.228.154; 1.I.228.157; 1.I.228.166; 1.I.228.169; 1.I.228.172; 1.I.228.175;
 1.I.228.240; 1.I.228.244; 1.I.229.228; 1.I.229.229; 1.I.229.230; 1.I.229.231; 1.I.229.236;
 1.I.229.237; 1.I.229.238; 1.I.229.239; 1.I.229.154; 1.I.229.157; 1.I.229.166; 1.I.229.169;
 1.I.229.172; 1.I.229.175; 1.I.229.240; 1.I.229.244; 1.I.230.228; 1.I.230.229; 1.I.230.230;
 1.I.230.231; 1.I.230.236; 1.I.230.237; 1.I.230.238; 1.I.230.239; 1.I.230.154; 1.I.230.157;
 40 1.I.230.166; 1.I.230.169; 1.I.230.172; 1.I.230.175; 1.I.230.240; 1.I.230.244; 1.I.231.228;
 1.I.231.229; 1.I.231.230; 1.I.231.231; 1.I.231.236; 1.I.231.237; 1.I.231.238; 1.I.231.239;
 1.I.231.154; 1.I.231.157; 1.I.231.166; 1.I.231.169; 1.I.231.172; 1.I.231.175; 1.I.231.240;
 1.I.231.244; 1.I.236.228; 1.I.236.229; 1.I.236.230; 1.I.236.231; 1.I.236.236; 1.I.236.237;
 1.I.236.238; 1.I.236.239; 1.I.236.154; 1.I.236.157; 1.I.236.166; 1.I.236.169; 1.I.236.172;
 45 1.I.236.175; 1.I.236.240; 1.I.236.244; 1.I.237.228; 1.I.237.229; 1.I.237.230; 1.I.237.231;
 1.I.237.236; 1.I.237.237; 1.I.237.238; 1.I.237.239; 1.I.237.154; 1.I.237.157; 1.I.237.166;

1.I.237.169; 1.I.237.172; 1.I.237.175; 1.I.237.240; 1.I.237.244; 1.I.238.228; 1.I.238.229;
 1.I.238.230; 1.I.238.231; 1.I.238.236; 1.I.238.237; 1.I.238.238; 1.I.238.239; 1.I.238.154;
 1.I.238.157; 1.I.238.166; 1.I.238.169; 1.I.238.172; 1.I.238.175; 1.I.238.240; 1.I.238.244;
 1.I.239.228; 1.I.239.229; 1.I.239.230; 1.I.239.231; 1.I.239.236; 1.I.239.237; 1.I.239.238;
 5 1.I.239.239; 1.I.239.154; 1.I.239.157; 1.I.239.166; 1.I.239.169; 1.I.239.172; 1.I.239.175;
 1.I.239.240; 1.I.239.244; 1.I.154.228; 1.I.154.229; 1.I.154.230; 1.I.154.231; 1.I.154.236;
 1.I.154.237; 1.I.154.238; 1.I.154.239; 1.I.154.154; 1.I.154.157; 1.I.154.166; 1.I.154.169;
 1.I.154.172; 1.I.154.175; 1.I.154.240; 1.I.154.244; 1.I.157.228; 1.I.157.229; 1.I.157.230;
 1.I.157.231; 1.I.157.236; 1.I.157.237; 1.I.157.238; 1.I.157.239; 1.I.157.154; 1.I.157.157;
 10 1.I.157.166; 1.I.157.169; 1.I.157.172; 1.I.157.175; 1.I.157.240; 1.I.157.244; 1.I.166.228;
 1.I.166.229; 1.I.166.230; 1.I.166.231; 1.I.166.236; 1.I.166.237; 1.I.166.238; 1.I.166.239;
 1.I.166.154; 1.I.166.157; 1.I.166.166; 1.I.166.169; 1.I.166.172; 1.I.166.175; 1.I.166.240;
 1.I.166.244; 1.I.169.228; 1.I.169.229; 1.I.169.230; 1.I.169.231; 1.I.169.236; 1.I.169.237;
 1.I.169.238; 1.I.169.239; 1.I.169.154; 1.I.169.157; 1.I.169.166; 1.I.169.169; 1.I.169.172;
 15 1.I.169.175; 1.I.169.240; 1.I.169.244; 1.I.172.228; 1.I.172.229; 1.I.172.230; 1.I.172.231;
 1.I.172.236; 1.I.172.237; 1.I.172.238; 1.I.172.239; 1.I.172.154; 1.I.172.157; 1.I.172.166;
 1.I.172.169; 1.I.172.172; 1.I.172.175; 1.I.172.240; 1.I.172.244; 1.I.175.228; 1.I.175.229;
 1.I.175.230; 1.I.175.231; 1.I.175.236; 1.I.175.237; 1.I.175.238; 1.I.175.239; 1.I.175.154;
 1.I.175.157; 1.I.175.166; 1.I.175.169; 1.I.175.172; 1.I.175.175; 1.I.175.240; 1.I.175.244;
 20 1.I.240.228; 1.I.240.229; 1.I.240.230; 1.I.240.231; 1.I.240.236; 1.I.240.237; 1.I.240.238;
 1.I.240.239; 1.I.240.154; 1.I.240.157; 1.I.240.166; 1.I.240.169; 1.I.240.172; 1.I.240.175;
 1.I.240.240; 1.I.240.244; 1.I.244.228; 1.I.244.229; 1.I.244.230; 1.I.244.231; 1.I.244.236;
 1.I.244.237; 1.I.244.238; 1.I.244.239; 1.I.244.154; 1.I.244.157; 1.I.244.166; 1.I.244.169;
 1.I.244.172; 1.I.244.175; 1.I.244.240; 1.I.244.244;

25

Prodrugs of 1.I

1.J.228.228; 1.J.228.229; 1.J.228.230; 1.J.228.231; 1.J.228.236; 1.J.228.237; 1.J.228.238;
 1.J.228.239; 1.J.228.154; 1.J.228.157; 1.J.228.166; 1.J.228.169; 1.J.228.172; 1.J.228.175;
 1.J.228.240; 1.J.228.244; 1.J.229.228; 1.J.229.229; 1.J.229.230; 1.J.229.231; 1.J.229.236;
 30 1.J.229.237; 1.J.229.238; 1.J.229.239; 1.J.229.154; 1.J.229.157; 1.J.229.166; 1.J.229.169;
 1.J.229.172; 1.J.229.175; 1.J.229.240; 1.J.229.244; 1.J.230.228; 1.J.230.229; 1.J.230.230;
 1.J.230.231; 1.J.230.236; 1.J.230.237; 1.J.230.238; 1.J.230.239; 1.J.230.154; 1.J.230.157;
 1.J.230.166; 1.J.230.169; 1.J.230.172; 1.J.230.175; 1.J.230.240; 1.J.230.244; 1.J.231.228;
 1.J.231.229; 1.J.231.230; 1.J.231.231; 1.J.231.236; 1.J.231.237; 1.J.231.238; 1.J.231.239;
 35 1.J.231.154; 1.J.231.157; 1.J.231.166; 1.J.231.169; 1.J.231.172; 1.J.231.175; 1.J.231.240;
 1.J.231.244; 1.J.236.228; 1.J.236.229; 1.J.236.230; 1.J.236.231; 1.J.236.236; 1.J.236.237;
 1.J.236.238; 1.J.236.239; 1.J.236.154; 1.J.236.157; 1.J.236.166; 1.J.236.169; 1.J.236.172;
 1.J.236.175; 1.J.236.240; 1.J.236.244; 1.J.237.228; 1.J.237.229; 1.J.237.230; 1.J.237.231;
 1.J.237.236; 1.J.237.237; 1.J.237.238; 1.J.237.239; 1.J.237.154; 1.J.237.157; 1.J.237.166;
 40 1.J.237.169; 1.J.237.172; 1.J.237.175; 1.J.237.240; 1.J.237.244; 1.J.238.228; 1.J.238.229;
 1.J.238.230; 1.J.238.231; 1.J.238.236; 1.J.238.237; 1.J.238.238; 1.J.238.239; 1.J.238.154;
 1.J.238.157; 1.J.238.166; 1.J.238.169; 1.J.238.172; 1.J.238.175; 1.J.238.240; 1.J.238.244;
 1.J.239.228; 1.J.239.229; 1.J.239.230; 1.J.239.231; 1.J.239.236; 1.J.239.237; 1.J.239.238;
 1.J.239.239; 1.J.239.154; 1.J.239.157; 1.J.239.166; 1.J.239.169; 1.J.239.172; 1.J.239.175;
 45 1.J.239.240; 1.J.239.244; 1.J.154.228; 1.J.154.229; 1.J.154.230; 1.J.154.231; 1.J.154.236;
 1.J.154.237; 1.J.154.238; 1.J.154.239; 1.J.154.154; 1.J.154.157; 1.J.154.166; 1.J.154.169;

- 1.J.154.172; 1.J.154.175; 1.J.154.240; 1.J.154.244; 1.J.157.228; 1.J.157.229; 1.J.157.230;
 1.J.157.231; 1.J.157.236; 1.J.157.237; 1.J.157.238; 1.J.157.239; 1.J.157.154; 1.J.157.157;
 1.J.157.166; 1.J.157.169; 1.J.157.172; 1.J.157.175; 1.J.157.240; 1.J.157.244; 1.J.166.228;
 1.J.166.229; 1.J.166.230; 1.J.166.231; 1.J.166.236; 1.J.166.237; 1.J.166.238; 1.J.166.239;
 5 1.J.166.154; 1.J.166.157; 1.J.166.166; 1.J.166.169; 1.J.166.172; 1.J.166.175; 1.J.166.240;
 1.J.166.244; 1.J.169.228; 1.J.169.229; 1.J.169.230; 1.J.169.231; 1.J.169.236; 1.J.169.237;
 1.J.169.238; 1.J.169.239; 1.J.169.154; 1.J.169.157; 1.J.169.166; 1.J.169.169; 1.J.169.172;
 1.J.169.175; 1.J.169.240; 1.J.169.244; 1.J.172.228; 1.J.172.229; 1.J.172.230; 1.J.172.231;
 1.J.172.236; 1.J.172.237; 1.J.172.238; 1.J.172.239; 1.J.172.154; 1.J.172.157; 1.J.172.166;
 10 1.J.172.169; 1.J.172.172; 1.J.172.175; 1.J.172.240; 1.J.172.244; 1.J.175.228; 1.J.175.229;
 1.J.175.230; 1.J.175.231; 1.J.175.236; 1.J.175.237; 1.J.175.238; 1.J.175.239; 1.J.175.154;
 1.J.175.157; 1.J.175.166; 1.J.175.169; 1.J.175.172; 1.J.175.175; 1.J.175.240; 1.J.175.244;
 1.J.240.228; 1.J.240.229; 1.J.240.230; 1.J.240.231; 1.J.240.236; 1.J.240.237; 1.J.240.238;
 1.J.240.239; 1.J.240.154; 1.J.240.157; 1.J.240.166; 1.J.240.169; 1.J.240.172; 1.J.240.175;
 15 1.J.240.240; 1.J.240.244; 1.J.244.228; 1.J.244.229; 1.J.244.230; 1.J.244.231; 1.J.244.236;
 1.J.244.237; 1.J.244.238; 1.J.244.239; 1.J.244.154; 1.J.244.157; 1.J.244.166; 1.J.244.169;
 1.J.244.172; 1.J.244.175; 1.J.244.240; 1.J.244.244;

Prodrugs of 1.L

- 20 1.L.228.228; 1.L.228.229; 1.L.228.230; 1.L.228.231; 1.L.228.236; 1.L.228.237;
 1.L.228.238; 1.L.228.239; 1.L.228.154; 1.L.228.157; 1.L.228.166; 1.L.228.169; 1.L.228.172;
 1.L.228.175; 1.L.228.240; 1.L.228.244; 1.L.229.228; 1.L.229.229; 1.L.229.230; 1.L.229.231;
 1.L.229.236; 1.L.229.237; 1.L.229.238; 1.L.229.239; 1.L.229.154; 1.L.229.157; 1.L.229.166;
 1.L.229.169; 1.L.229.172; 1.L.229.175; 1.L.229.240; 1.L.229.244; 1.L.230.228; 1.L.230.229;
 25 1.L.230.230; 1.L.230.231; 1.L.230.236; 1.L.230.237; 1.L.230.238; 1.L.230.239; 1.L.230.154;
 1.L.230.157; 1.L.230.166; 1.L.230.169; 1.L.230.172; 1.L.230.175; 1.L.230.240; 1.L.230.244;
 1.L.231.228; 1.L.231.229; 1.L.231.230; 1.L.231.231; 1.L.231.236; 1.L.231.237; 1.L.231.238;
 1.L.231.239; 1.L.231.154; 1.L.231.157; 1.L.231.166; 1.L.231.169; 1.L.231.172; 1.L.231.175;
 1.L.231.240; 1.L.231.244; 1.L.236.228; 1.L.236.229; 1.L.236.230; 1.L.236.231; 1.L.236.236;
 30 1.L.236.237; 1.L.236.238; 1.L.236.239; 1.L.236.154; 1.L.236.157; 1.L.236.166; 1.L.236.169;
 1.L.236.172; 1.L.236.175; 1.L.236.240; 1.L.236.244; 1.L.237.228; 1.L.237.229; 1.L.237.230;
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 1.L.238.229; 1.L.238.230; 1.L.238.231; 1.L.238.236; 1.L.238.237; 1.L.238.238; 1.L.238.239;
 35 1.L.238.154; 1.L.238.157; 1.L.238.166; 1.L.238.169; 1.L.238.172; 1.L.238.175; 1.L.238.240;
 1.L.238.244; 1.L.239.228; 1.L.239.229; 1.L.239.230; 1.L.239.231; 1.L.239.236; 1.L.239.237;
 1.L.239.238; 1.L.239.239; 1.L.239.154; 1.L.239.157; 1.L.239.166; 1.L.239.169; 1.L.239.172;
 1.L.239.175; 1.L.239.240; 1.L.239.244; 1.L.154.228; 1.L.154.229; 1.L.154.230; 1.L.154.231;
 1.L.154.236; 1.L.154.237; 1.L.154.238; 1.L.154.239; 1.L.154.154; 1.L.154.157; 1.L.154.166;
 40 1.L.154.169; 1.L.154.172; 1.L.154.175; 1.L.154.240; 1.L.154.244; 1.L.157.228; 1.L.157.229;
 1.L.157.230; 1.L.157.231; 1.L.157.236; 1.L.157.237; 1.L.157.238; 1.L.157.239; 1.L.157.154;
 1.L.157.157; 1.L.157.166; 1.L.157.169; 1.L.157.172; 1.L.157.175; 1.L.157.240; 1.L.157.244;
 1.L.166.228; 1.L.166.229; 1.L.166.230; 1.L.166.231; 1.L.166.236; 1.L.166.237; 1.L.166.238;
 1.L.166.239; 1.L.166.154; 1.L.166.157; 1.L.166.166; 1.L.166.169; 1.L.166.172; 1.L.166.175;
 45 1.L.166.240; 1.L.166.244; 1.L.169.228; 1.L.169.229; 1.L.169.230; 1.L.169.231; 1.L.169.236;
 1.L.169.237; 1.L.169.238; 1.L.169.239; 1.L.169.154; 1.L.169.157; 1.L.169.166; 1.L.169.169;

1.L.169.172; 1.L.169.175; 1.L.169.240; 1.L.169.244; 1.L.172.228; 1.L.172.229; 1.L.172.230;
 1.L.172.231; 1.L.172.236; 1.L.172.237; 1.L.172.238; 1.L.172.239; 1.L.172.154; 1.L.172.157;
 1.L.172.166; 1.L.172.169; 1.L.172.172; 1.L.172.175; 1.L.172.240; 1.L.172.244; 1.L.175.228;
 1.L.175.229; 1.L.175.230; 1.L.175.231; 1.L.175.236; 1.L.175.237; 1.L.175.238; 1.L.175.239;
 5 1.L.175.154; 1.L.175.157; 1.L.175.166; 1.L.175.169; 1.L.175.172; 1.L.175.175; 1.L.175.240;
 1.L.175.244; 1.L.240.228; 1.L.240.229; 1.L.240.230; 1.L.240.231; 1.L.240.236; 1.L.240.237;
 1.L.240.238; 1.L.240.239; 1.L.240.154; 1.L.240.157; 1.L.240.166; 1.L.240.169; 1.L.240.172;
 1.L.240.175; 1.L.240.240; 1.L.240.244; 1.L.244.228; 1.L.244.229; 1.L.244.230; 1.L.244.231;
 1.L.244.236; 1.L.244.237; 1.L.244.238; 1.L.244.239; 1.L.244.154; 1.L.244.157; 1.L.244.166;
 10 1.L.244.169; 1.L.244.172; 1.L.244.175; 1.L.244.240; 1.L.244.244;

Prodrugs of 1.O

1.O.228.228; 1.O.228.229; 1.O.228.230; 1.O.228.231; 1.O.228.236; 1.O.228.237;
 1.O.228.238; 1.O.228.239; 1.O.228.154; 1.O.228.157; 1.O.228.166; 1.O.228.169;
 15 1.O.228.172; 1.O.228.175; 1.O.228.240; 1.O.228.244; 1.O.229.228; 1.O.229.229;
 1.O.229.230; 1.O.229.231; 1.O.229.236; 1.O.229.237; 1.O.229.238; 1.O.229.239;
 1.O.229.154; 1.O.229.157; 1.O.229.166; 1.O.229.169; 1.O.229.172; 1.O.229.175;
 1.O.229.240; 1.O.229.244; 1.O.230.228; 1.O.230.229; 1.O.230.230; 1.O.230.231;
 1.O.230.236; 1.O.230.237; 1.O.230.238; 1.O.230.239; 1.O.230.154; 1.O.230.157;
 20 1.O.230.166; 1.O.230.169; 1.O.230.172; 1.O.230.175; 1.O.230.240; 1.O.230.244;
 1.O.231.228; 1.O.231.229; 1.O.231.230; 1.O.231.231; 1.O.231.236; 1.O.231.237;
 1.O.231.238; 1.O.231.239; 1.O.231.154; 1.O.231.157; 1.O.231.166; 1.O.231.169;
 1.O.231.172; 1.O.231.175; 1.O.231.240; 1.O.231.244; 1.O.236.228; 1.O.236.229;
 1.O.236.230; 1.O.236.231; 1.O.236.236; 1.O.236.237; 1.O.236.238; 1.O.236.239;
 25 1.O.236.154; 1.O.236.157; 1.O.236.166; 1.O.236.169; 1.O.236.172; 1.O.236.175;
 1.O.236.240; 1.O.236.244; 1.O.237.228; 1.O.237.229; 1.O.237.230; 1.O.237.231;
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 1.O.237.166; 1.O.237.169; 1.O.237.172; 1.O.237.175; 1.O.237.240; 1.O.237.244;
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 30 1.O.238.238; 1.O.238.239; 1.O.238.154; 1.O.238.157; 1.O.238.166; 1.O.238.169;
 1.O.238.172; 1.O.238.175; 1.O.238.240; 1.O.238.244; 1.O.239.228; 1.O.239.229;
 1.O.239.230; 1.O.239.231; 1.O.239.236; 1.O.239.237; 1.O.239.238; 1.O.239.239;
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 35 1.O.154.236; 1.O.154.237; 1.O.154.238; 1.O.154.239; 1.O.154.154; 1.O.154.157;
 1.O.154.166; 1.O.154.169; 1.O.154.172; 1.O.154.175; 1.O.154.240; 1.O.154.244;
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 1.O.157.238; 1.O.157.239; 1.O.157.154; 1.O.157.157; 1.O.157.166; 1.O.157.169;
 1.O.157.172; 1.O.157.175; 1.O.157.240; 1.O.157.244; 1.O.166.228; 1.O.166.229;
 40 1.O.166.230; 1.O.166.231; 1.O.166.236; 1.O.166.237; 1.O.166.238; 1.O.166.239;
 1.O.166.154; 1.O.166.157; 1.O.166.166; 1.O.166.169; 1.O.166.172; 1.O.166.175;
 1.O.166.240; 1.O.166.244; 1.O.169.228; 1.O.169.229; 1.O.169.230; 1.O.169.231;
 1.O.169.236; 1.O.169.237; 1.O.169.238; 1.O.169.239; 1.O.169.154; 1.O.169.157;
 1.O.169.166; 1.O.169.169; 1.O.169.172; 1.O.169.175; 1.O.169.240; 1.O.169.244;
 45 1.O.172.228; 1.O.172.229; 1.O.172.230; 1.O.172.231; 1.O.172.236; 1.O.172.237;
 1.O.172.238; 1.O.172.239; 1.O.172.154; 1.O.172.157; 1.O.172.166; 1.O.172.169;

1.O.172.172; 1.O.172.175; 1.O.172.240; 1.O.172.244; 1.O.175.228; 1.O.175.229;
1.O.175.230; 1.O.175.231; 1.O.175.236; 1.O.175.237; 1.O.175.238; 1.O.175.239;
1.O.175.154; 1.O.175.157; 1.O.175.166; 1.O.175.169; 1.O.175.172; 1.O.175.175;
1.O.175.240; 1.O.175.244; 1.O.240.228; 1.O.240.229; 1.O.240.230; 1.O.240.231;
5 1.O.240.236; 1.O.240.237; 1.O.240.238; 1.O.240.239; 1.O.240.154; 1.O.240.157;
1.O.240.166; 1.O.240.169; 1.O.240.172; 1.O.240.175; 1.O.240.240; 1.O.240.244;
1.O.244.228; 1.O.244.229; 1.O.244.230; 1.O.244.231; 1.O.244.236; 1.O.244.237;
1.O.244.238; 1.O.244.239; 1.O.244.154; 1.O.244.157; 1.O.244.166; 1.O.244.169;
1.O.244.172; 1.O.244.175; 1.O.244.240; 1.O.244.244;

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Prodrugs of 1.P

1.P.228.228; 1.P.228.229; 1.P.228.230; 1.P.228.231; 1.P.228.236; 1.P.228.237;
1.P.228.238; 1.P.228.239; 1.P.228.154; 1.P.228.157; 1.P.228.166; 1.P.228.169; 1.P.228.172;
1.P.228.175; 1.P.228.240; 1.P.228.244; 1.P.229.228; 1.P.229.229; 1.P.229.230; 1.P.229.231;
15 1.P.229.236; 1.P.229.237; 1.P.229.238; 1.P.229.239; 1.P.229.154; 1.P.229.157; 1.P.229.166;
1.P.229.169; 1.P.229.172; 1.P.229.175; 1.P.229.240; 1.P.229.244; 1.P.230.228; 1.P.230.229;
1.P.230.230; 1.P.230.231; 1.P.230.236; 1.P.230.237; 1.P.230.238; 1.P.230.239; 1.P.230.154;
1.P.230.157; 1.P.230.166; 1.P.230.169; 1.P.230.172; 1.P.230.175; 1.P.230.240; 1.P.230.244;
1.P.231.228; 1.P.231.229; 1.P.231.230; 1.P.231.231; 1.P.231.236; 1.P.231.237; 1.P.231.238;
20 1.P.231.239; 1.P.231.154; 1.P.231.157; 1.P.231.166; 1.P.231.169; 1.P.231.172; 1.P.231.175;
1.P.231.240; 1.P.231.244; 1.P.236.228; 1.P.236.229; 1.P.236.230; 1.P.236.231; 1.P.236.236;
1.P.236.237; 1.P.236.238; 1.P.236.239; 1.P.236.154; 1.P.236.157; 1.P.236.166; 1.P.236.169;
1.P.236.172; 1.P.236.175; 1.P.236.240; 1.P.236.244; 1.P.237.228; 1.P.237.229; 1.P.237.230;
1.P.237.231; 1.P.237.236; 1.P.237.237; 1.P.237.238; 1.P.237.239; 1.P.237.154; 1.P.237.157;
25 1.P.237.166; 1.P.237.169; 1.P.237.172; 1.P.237.175; 1.P.237.240; 1.P.237.244; 1.P.238.228;
1.P.238.229; 1.P.238.230; 1.P.238.231; 1.P.238.236; 1.P.238.237; 1.P.238.238; 1.P.238.239;
1.P.238.154; 1.P.238.157; 1.P.238.166; 1.P.238.169; 1.P.238.172; 1.P.238.175; 1.P.238.240;
1.P.238.244; 1.P.239.228; 1.P.239.229; 1.P.239.230; 1.P.239.231; 1.P.239.236; 1.P.239.237;
1.P.239.238; 1.P.239.239; 1.P.239.154; 1.P.239.157; 1.P.239.166; 1.P.239.169; 1.P.239.172;
30 1.P.239.175; 1.P.239.240; 1.P.239.244; 1.P.154.228; 1.P.154.229; 1.P.154.230; 1.P.154.231;
1.P.154.236; 1.P.154.237; 1.P.154.238; 1.P.154.239; 1.P.154.154; 1.P.154.157; 1.P.154.166;
1.P.154.169; 1.P.154.172; 1.P.154.175; 1.P.154.240; 1.P.154.244; 1.P.157.228; 1.P.157.229;
1.P.157.230; 1.P.157.231; 1.P.157.236; 1.P.157.237; 1.P.157.238; 1.P.157.239; 1.P.157.154;
1.P.157.157; 1.P.157.166; 1.P.157.169; 1.P.157.172; 1.P.157.175; 1.P.157.240; 1.P.157.244;
35 1.P.166.228; 1.P.166.229; 1.P.166.230; 1.P.166.231; 1.P.166.236; 1.P.166.237; 1.P.166.238;
1.P.166.239; 1.P.166.154; 1.P.166.157; 1.P.166.166; 1.P.166.169; 1.P.166.172; 1.P.166.175;
1.P.166.240; 1.P.166.244; 1.P.169.228; 1.P.169.229; 1.P.169.230; 1.P.169.231; 1.P.169.236;
1.P.169.237; 1.P.169.238; 1.P.169.239; 1.P.169.154; 1.P.169.157; 1.P.169.166; 1.P.169.169;
1.P.169.172; 1.P.169.175; 1.P.169.240; 1.P.169.244; 1.P.172.228; 1.P.172.229; 1.P.172.230;
40 1.P.172.231; 1.P.172.236; 1.P.172.237; 1.P.172.238; 1.P.172.239; 1.P.172.154; 1.P.172.157;
1.P.172.166; 1.P.172.169; 1.P.172.172; 1.P.172.175; 1.P.172.240; 1.P.172.244; 1.P.175.228;
1.P.175.229; 1.P.175.230; 1.P.175.231; 1.P.175.236; 1.P.175.237; 1.P.175.238; 1.P.175.239;
1.P.175.154; 1.P.175.157; 1.P.175.166; 1.P.175.169; 1.P.175.172; 1.P.175.175; 1.P.175.240;
1.P.175.244; 1.P.240.228; 1.P.240.229; 1.P.240.230; 1.P.240.231; 1.P.240.236; 1.P.240.237;
45 1.P.240.238; 1.P.240.239; 1.P.240.154; 1.P.240.157; 1.P.240.166; 1.P.240.169; 1.P.240.172;
1.P.240.175; 1.P.240.240; 1.P.240.244; 1.P.244.228; 1.P.244.229; 1.P.244.230; 1.P.244.231;

1.P.244.236; 1.P.244.237; 1.P.244.238; 1.P.244.239; 1.P.244.154; 1.P.244.157; 1.P.244.166;
1.P.244.169; 1.P.244.172; 1.P.244.175; 1.P.244.240; 1.P.244.244;

Prodrugs of 1.U

- 5 1.U.228.228; 1.U.228.229; 1.U.228.230; 1.U.228.231; 1.U.228.236; 1.U.228.237;
1.U.228.238; 1.U.228.239; 1.U.228.154; 1.U.228.157; 1.U.228.166; 1.U.228.169;
1.U.228.172; 1.U.228.175; 1.U.228.240; 1.U.228.244; 1.U.229.228; 1.U.229.229;
1.U.229.230; 1.U.229.231; 1.U.229.236; 1.U.229.237; 1.U.229.238; 1.U.229.239;
1.U.229.154; 1.U.229.157; 1.U.229.166; 1.U.229.169; 1.U.229.172; 1.U.229.175;
10 1.U.229.240; 1.U.229.244; 1.U.230.228; 1.U.230.229; 1.U.230.230; 1.U.230.231;
1.U.230.236; 1.U.230.237; 1.U.230.238; 1.U.230.239; 1.U.230.154; 1.U.230.157;
1.U.230.166; 1.U.230.169; 1.U.230.172; 1.U.230.175; 1.U.230.240; 1.U.230.244;
1.U.231.228; 1.U.231.229; 1.U.231.230; 1.U.231.231; 1.U.231.236; 1.U.231.237;
1.U.231.238; 1.U.231.239; 1.U.231.154; 1.U.231.157; 1.U.231.166; 1.U.231.169;
15 1.U.231.172; 1.U.231.175; 1.U.231.240; 1.U.231.244; 1.U.236.228; 1.U.236.229;
1.U.236.230; 1.U.236.231; 1.U.236.236; 1.U.236.237; 1.U.236.238; 1.U.236.239;
1.U.236.154; 1.U.236.157; 1.U.236.166; 1.U.236.169; 1.U.236.172; 1.U.236.175;
1.U.236.240; 1.U.236.244; 1.U.237.228; 1.U.237.229; 1.U.237.230; 1.U.237.231;
1.U.237.236; 1.U.237.237; 1.U.237.238; 1.U.237.239; 1.U.237.154; 1.U.237.157;
20 1.U.237.166; 1.U.237.169; 1.U.237.172; 1.U.237.175; 1.U.237.240; 1.U.237.244;
1.U.238.228; 1.U.238.229; 1.U.238.230; 1.U.238.231; 1.U.238.236; 1.U.238.237;
1.U.238.238; 1.U.238.239; 1.U.238.154; 1.U.238.157; 1.U.238.166; 1.U.238.169;
1.U.238.172; 1.U.238.175; 1.U.238.240; 1.U.238.244; 1.U.239.228; 1.U.239.229;
1.U.239.230; 1.U.239.231; 1.U.239.236; 1.U.239.237; 1.U.239.238; 1.U.239.239;
25 1.U.239.154; 1.U.239.157; 1.U.239.166; 1.U.239.169; 1.U.239.172; 1.U.239.175;
1.U.239.240; 1.U.239.244; 1.U.154.228; 1.U.154.229; 1.U.154.230; 1.U.154.231;
1.U.154.236; 1.U.154.237; 1.U.154.238; 1.U.154.239; 1.U.154.154; 1.U.154.157;
1.U.154.166; 1.U.154.169; 1.U.154.172; 1.U.154.175; 1.U.154.240; 1.U.154.244;
1.U.157.228; 1.U.157.229; 1.U.157.230; 1.U.157.231; 1.U.157.236; 1.U.157.237;
30 1.U.157.238; 1.U.157.239; 1.U.157.154; 1.U.157.157; 1.U.157.166; 1.U.157.169;
1.U.157.172; 1.U.157.175; 1.U.157.240; 1.U.157.244; 1.U.166.228; 1.U.166.229;
1.U.166.230; 1.U.166.231; 1.U.166.236; 1.U.166.237; 1.U.166.238; 1.U.166.239;
1.U.166.154; 1.U.166.157; 1.U.166.166; 1.U.166.169; 1.U.166.172; 1.U.166.175;
1.U.166.240; 1.U.166.244; 1.U.169.228; 1.U.169.229; 1.U.169.230; 1.U.169.231;
35 1.U.169.236; 1.U.169.237; 1.U.169.238; 1.U.169.239; 1.U.169.154; 1.U.169.157;
1.U.169.166; 1.U.169.169; 1.U.169.172; 1.U.169.175; 1.U.169.240; 1.U.169.244;
1.U.172.228; 1.U.172.229; 1.U.172.230; 1.U.172.231; 1.U.172.236; 1.U.172.237;
1.U.172.238; 1.U.172.239; 1.U.172.154; 1.U.172.157; 1.U.172.166; 1.U.172.169;
1.U.172.172; 1.U.172.175; 1.U.172.240; 1.U.172.244; 1.U.175.228; 1.U.175.229;
40 1.U.175.230; 1.U.175.231; 1.U.175.236; 1.U.175.237; 1.U.175.238; 1.U.175.239;
1.U.175.154; 1.U.175.157; 1.U.175.166; 1.U.175.169; 1.U.175.172; 1.U.175.175;
1.U.175.240; 1.U.175.244; 1.U.240.228; 1.U.240.229; 1.U.240.230; 1.U.240.231;
1.U.240.236; 1.U.240.237; 1.U.240.238; 1.U.240.239; 1.U.240.154; 1.U.240.157;
1.U.240.166; 1.U.240.169; 1.U.240.172; 1.U.240.175; 1.U.240.240; 1.U.240.244;
45 1.U.244.228; 1.U.244.229; 1.U.244.230; 1.U.244.231; 1.U.244.236; 1.U.244.237;

1.U.244.238; 1.U.244.239; 1.U.244.154; 1.U.244.157; 1.U.244.166; 1.U.244.169;
1.U.244.172; 1.U.244.175; 1.U.244.240; 1.U.244.244;

Prodrugs of 1.W

- 5 1.W.228.228; 1.W.228.229; 1.W.228.230; 1.W.228.231; 1.W.228.236; 1.W.228.237;
1.W.228.238; 1.W.228.239; 1.W.228.154; 1.W.228.157; 1.W.228.166; 1.W.228.169;
1.W.228.172; 1.W.228.175; 1.W.228.240; 1.W.228.244; 1.W.229.228; 1.W.229.229;
1.W.229.230; 1.W.229.231; 1.W.229.236; 1.W.229.237; 1.W.229.238; 1.W.229.239;
1.W.229.154; 1.W.229.157; 1.W.229.166; 1.W.229.169; 1.W.229.172; 1.W.229.175;
10 1.W.229.240; 1.W.229.244; 1.W.230.228; 1.W.230.229; 1.W.230.230; 1.W.230.231;
1.W.230.236; 1.W.230.237; 1.W.230.238; 1.W.230.239; 1.W.230.154; 1.W.230.157;
1.W.230.166; 1.W.230.169; 1.W.230.172; 1.W.230.175; 1.W.230.240; 1.W.230.244;
1.W.231.228; 1.W.231.229; 1.W.231.230; 1.W.231.231; 1.W.231.236; 1.W.231.237;
1.W.231.238; 1.W.231.239; 1.W.231.154; 1.W.231.157; 1.W.231.166; 1.W.231.169;
15 1.W.231.172; 1.W.231.175; 1.W.231.240; 1.W.231.244; 1.W.236.228; 1.W.236.229;
1.W.236.230; 1.W.236.231; 1.W.236.236; 1.W.236.237; 1.W.236.238; 1.W.236.239;
1.W.236.154; 1.W.236.157; 1.W.236.166; 1.W.236.169; 1.W.236.172; 1.W.236.175;
1.W.236.240; 1.W.236.244; 1.W.237.228; 1.W.237.229; 1.W.237.230; 1.W.237.231;
1.W.237.236; 1.W.237.237; 1.W.237.238; 1.W.237.239; 1.W.237.154; 1.W.237.157;
20 1.W.237.166; 1.W.237.169; 1.W.237.172; 1.W.237.175; 1.W.237.240; 1.W.237.244;
1.W.238.228; 1.W.238.229; 1.W.238.230; 1.W.238.231; 1.W.238.236; 1.W.238.237;
1.W.238.238; 1.W.238.239; 1.W.238.154; 1.W.238.157; 1.W.238.166; 1.W.238.169;
1.W.238.172; 1.W.238.175; 1.W.238.240; 1.W.238.244; 1.W.239.228; 1.W.239.229;
1.W.239.230; 1.W.239.231; 1.W.239.236; 1.W.239.237; 1.W.239.238; 1.W.239.239;
25 1.W.239.154; 1.W.239.157; 1.W.239.166; 1.W.239.169; 1.W.239.172; 1.W.239.175;
1.W.239.240; 1.W.239.244; 1.W.154.228; 1.W.154.229; 1.W.154.230; 1.W.154.231;
1.W.154.236; 1.W.154.237; 1.W.154.238; 1.W.154.239; 1.W.154.154; 1.W.154.157;
1.W.154.166; 1.W.154.169; 1.W.154.172; 1.W.154.175; 1.W.154.240; 1.W.154.244;
1.W.157.228; 1.W.157.229; 1.W.157.230; 1.W.157.231; 1.W.157.236; 1.W.157.237;
30 1.W.157.238; 1.W.157.239; 1.W.157.154; 1.W.157.157; 1.W.157.166; 1.W.157.169;
1.W.157.172; 1.W.157.175; 1.W.157.240; 1.W.157.244; 1.W.166.228; 1.W.166.229;
1.W.166.230; 1.W.166.231; 1.W.166.236; 1.W.166.237; 1.W.166.238; 1.W.166.239;
1.W.166.154; 1.W.166.157; 1.W.166.166; 1.W.166.169; 1.W.166.172; 1.W.166.175;
1.W.166.240; 1.W.166.244; 1.W.169.228; 1.W.169.229; 1.W.169.230; 1.W.169.231;
35 1.W.169.236; 1.W.169.237; 1.W.169.238; 1.W.169.239; 1.W.169.154; 1.W.169.157;
1.W.169.166; 1.W.169.169; 1.W.169.172; 1.W.169.175; 1.W.169.240; 1.W.169.244;
1.W.172.228; 1.W.172.229; 1.W.172.230; 1.W.172.231; 1.W.172.236; 1.W.172.237;
1.W.172.238; 1.W.172.239; 1.W.172.154; 1.W.172.157; 1.W.172.166; 1.W.172.169;
1.W.172.172; 1.W.172.175; 1.W.172.240; 1.W.172.244; 1.W.175.228; 1.W.175.229;
40 1.W.175.230; 1.W.175.231; 1.W.175.236; 1.W.175.237; 1.W.175.238; 1.W.175.239;
1.W.175.154; 1.W.175.157; 1.W.175.166; 1.W.175.169; 1.W.175.172; 1.W.175.175;
1.W.175.240; 1.W.175.244; 1.W.240.228; 1.W.240.229; 1.W.240.230; 1.W.240.231;
1.W.240.236; 1.W.240.237; 1.W.240.238; 1.W.240.239; 1.W.240.154; 1.W.240.157;
1.W.240.166; 1.W.240.169; 1.W.240.172; 1.W.240.175; 1.W.240.240; 1.W.240.244;
45 1.W.244.228; 1.W.244.229; 1.W.244.230; 1.W.244.231; 1.W.244.236; 1.W.244.237;

1.W.244.238; 1.W.244.239; 1.W.244.154; 1.W.244.157; 1.W.244.166; 1.W.244.169;
1.W.244.172; 1.W.244.175; 1.W.244.240; 1.W.244.244;

Prodrugs of 1.Y

- 5 1.Y.228.228; 1.Y.228.229; 1.Y.228.230; 1.Y.228.231; 1.Y.228.236; 1.Y.228.237;
1.Y.228.238; 1.Y.228.239; 1.Y.228.154; 1.Y.228.157; 1.Y.228.166; 1.Y.228.169;
1.Y.228.172; 1.Y.228.175; 1.Y.228.240; 1.Y.228.244; 1.Y.229.228; 1.Y.229.229;
1.Y.229.230; 1.Y.229.231; 1.Y.229.236; 1.Y.229.237; 1.Y.229.238; 1.Y.229.239;
1.Y.229.154; 1.Y.229.157; 1.Y.229.166; 1.Y.229.169; 1.Y.229.172; 1.Y.229.175;
10 1.Y.229.240; 1.Y.229.244; 1.Y.230.228; 1.Y.230.229; 1.Y.230.230; 1.Y.230.231;
1.Y.230.236; 1.Y.230.237; 1.Y.230.238; 1.Y.230.239; 1.Y.230.154; 1.Y.230.157;
1.Y.230.166; 1.Y.230.169; 1.Y.230.172; 1.Y.230.175; 1.Y.230.240; 1.Y.230.244;
1.Y.231.228; 1.Y.231.229; 1.Y.231.230; 1.Y.231.231; 1.Y.231.236; 1.Y.231.237;
1.Y.231.238; 1.Y.231.239; 1.Y.231.154; 1.Y.231.157; 1.Y.231.166; 1.Y.231.169;
15 1.Y.231.172; 1.Y.231.175; 1.Y.231.240; 1.Y.231.244; 1.Y.236.228; 1.Y.236.229;
1.Y.236.230; 1.Y.236.231; 1.Y.236.236; 1.Y.236.237; 1.Y.236.238; 1.Y.236.239;
1.Y.236.154; 1.Y.236.157; 1.Y.236.166; 1.Y.236.169; 1.Y.236.172; 1.Y.236.175;
1.Y.236.240; 1.Y.236.244; 1.Y.237.228; 1.Y.237.229; 1.Y.237.230; 1.Y.237.231;
1.Y.237.236; 1.Y.237.237; 1.Y.237.238; 1.Y.237.239; 1.Y.237.154; 1.Y.237.157;
20 1.Y.237.166; 1.Y.237.169; 1.Y.237.172; 1.Y.237.175; 1.Y.237.240; 1.Y.237.244;
1.Y.238.228; 1.Y.238.229; 1.Y.238.230; 1.Y.238.231; 1.Y.238.236; 1.Y.238.237;
1.Y.238.238; 1.Y.238.239; 1.Y.238.154; 1.Y.238.157; 1.Y.238.166; 1.Y.238.169;
1.Y.238.172; 1.Y.238.175; 1.Y.238.240; 1.Y.238.244; 1.Y.239.228; 1.Y.239.229;
1.Y.239.230; 1.Y.239.231; 1.Y.239.236; 1.Y.239.237; 1.Y.239.238; 1.Y.239.239;
25 1.Y.239.154; 1.Y.239.157; 1.Y.239.166; 1.Y.239.169; 1.Y.239.172; 1.Y.239.175;
1.Y.239.240; 1.Y.239.244; 1.Y.154.228; 1.Y.154.229; 1.Y.154.230; 1.Y.154.231;
1.Y.154.236; 1.Y.154.237; 1.Y.154.238; 1.Y.154.239; 1.Y.154.154; 1.Y.154.157;
1.Y.154.166; 1.Y.154.169; 1.Y.154.172; 1.Y.154.175; 1.Y.154.240; 1.Y.154.244;
1.Y.157.228; 1.Y.157.229; 1.Y.157.230; 1.Y.157.231; 1.Y.157.236; 1.Y.157.237;
30 1.Y.157.238; 1.Y.157.239; 1.Y.157.154; 1.Y.157.157; 1.Y.157.166; 1.Y.157.169;
1.Y.157.172; 1.Y.157.175; 1.Y.157.240; 1.Y.157.244; 1.Y.166.228; 1.Y.166.229;
1.Y.166.230; 1.Y.166.231; 1.Y.166.236; 1.Y.166.237; 1.Y.166.238; 1.Y.166.239;
1.Y.166.154; 1.Y.166.157; 1.Y.166.166; 1.Y.166.169; 1.Y.166.172; 1.Y.166.175;
1.Y.166.240; 1.Y.166.244; 1.Y.169.228; 1.Y.169.229; 1.Y.169.230; 1.Y.169.231;
35 1.Y.169.236; 1.Y.169.237; 1.Y.169.238; 1.Y.169.239; 1.Y.169.154; 1.Y.169.157;
1.Y.169.166; 1.Y.169.169; 1.Y.169.172; 1.Y.169.175; 1.Y.169.240; 1.Y.169.244;
1.Y.172.228; 1.Y.172.229; 1.Y.172.230; 1.Y.172.231; 1.Y.172.236; 1.Y.172.237;
1.Y.172.238; 1.Y.172.239; 1.Y.172.154; 1.Y.172.157; 1.Y.172.166; 1.Y.172.169;
1.Y.172.172; 1.Y.172.175; 1.Y.172.240; 1.Y.172.244; 1.Y.175.228; 1.Y.175.229;
40 1.Y.175.230; 1.Y.175.231; 1.Y.175.236; 1.Y.175.237; 1.Y.175.238; 1.Y.175.239;
1.Y.175.154; 1.Y.175.157; 1.Y.175.166; 1.Y.175.169; 1.Y.175.172; 1.Y.175.175;
1.Y.175.240; 1.Y.175.244; 1.Y.240.228; 1.Y.240.229; 1.Y.240.230; 1.Y.240.231;
1.Y.240.236; 1.Y.240.237; 1.Y.240.238; 1.Y.240.239; 1.Y.240.154; 1.Y.240.157;
1.Y.240.166; 1.Y.240.169; 1.Y.240.172; 1.Y.240.175; 1.Y.240.240; 1.Y.240.244;
45 1.Y.244.228; 1.Y.244.229; 1.Y.244.230; 1.Y.244.231; 1.Y.244.236; 1.Y.244.237;

1.Y.244.238; 1.Y.244.239; 1.Y.244.154; 1.Y.244.157; 1.Y.244.166; 1.Y.244.169;
1.Y.244.172; 1.Y.244.175; 1.Y.244.240; 1.Y.244.244;

Prodrugs of 2.B

- 5 2.B.228.228; 2.B.228.229; 2.B.228.230; 2.B.228.231; 2.B.228.236; 2.B.228.237;
2.B.228.238; 2.B.228.239; 2.B.228.154; 2.B.228.157; 2.B.228.166; 2.B.228.169; 2.B.228.172;
2.B.228.175; 2.B.228.240; 2.B.228.244; 2.B.229.228; 2.B.229.229; 2.B.229.230; 2.B.229.231;
2.B.229.236; 2.B.229.237; 2.B.229.238; 2.B.229.239; 2.B.229.154; 2.B.229.157; 2.B.229.166;
2.B.229.169; 2.B.229.172; 2.B.229.175; 2.B.229.240; 2.B.229.244; 2.B.230.228; 2.B.230.229;
10 2.B.230.230; 2.B.230.231; 2.B.230.236; 2.B.230.237; 2.B.230.238; 2.B.230.239; 2.B.230.154;
2.B.230.157; 2.B.230.166; 2.B.230.169; 2.B.230.172; 2.B.230.175; 2.B.230.240; 2.B.230.244;
2.B.231.228; 2.B.231.229; 2.B.231.230; 2.B.231.231; 2.B.231.236; 2.B.231.237; 2.B.231.238;
2.B.231.239; 2.B.231.154; 2.B.231.157; 2.B.231.166; 2.B.231.169; 2.B.231.172; 2.B.231.175;
2.B.231.240; 2.B.231.244; 2.B.236.228; 2.B.236.229; 2.B.236.230; 2.B.236.231; 2.B.236.236;
15 2.B.236.237; 2.B.236.238; 2.B.236.239; 2.B.236.154; 2.B.236.157; 2.B.236.166; 2.B.236.169;
2.B.236.172; 2.B.236.175; 2.B.236.240; 2.B.236.244; 2.B.237.228; 2.B.237.229; 2.B.237.230;
2.B.237.231; 2.B.237.236; 2.B.237.237; 2.B.237.238; 2.B.237.239; 2.B.237.154; 2.B.237.157;
2.B.237.166; 2.B.237.169; 2.B.237.172; 2.B.237.175; 2.B.237.240; 2.B.237.244; 2.B.238.228;
2.B.238.229; 2.B.238.230; 2.B.238.231; 2.B.238.236; 2.B.238.237; 2.B.238.238; 2.B.238.239;
20 2.B.238.154; 2.B.238.157; 2.B.238.166; 2.B.238.169; 2.B.238.172; 2.B.238.175; 2.B.238.240;
2.B.238.244; 2.B.239.228; 2.B.239.229; 2.B.239.230; 2.B.239.231; 2.B.239.236; 2.B.239.237;
2.B.239.238; 2.B.239.239; 2.B.239.154; 2.B.239.157; 2.B.239.166; 2.B.239.169; 2.B.239.172;
2.B.239.175; 2.B.239.240; 2.B.239.244; 2.B.154.228; 2.B.154.229; 2.B.154.230; 2.B.154.231;
2.B.154.236; 2.B.154.237; 2.B.154.238; 2.B.154.239; 2.B.154.154; 2.B.154.157; 2.B.154.166;
25 2.B.154.169; 2.B.154.172; 2.B.154.175; 2.B.154.240; 2.B.154.244; 2.B.157.228; 2.B.157.229;
2.B.157.230; 2.B.157.231; 2.B.157.236; 2.B.157.237; 2.B.157.238; 2.B.157.239; 2.B.157.154;
2.B.157.157; 2.B.157.166; 2.B.157.169; 2.B.157.172; 2.B.157.175; 2.B.157.240; 2.B.157.244;
2.B.166.228; 2.B.166.229; 2.B.166.230; 2.B.166.231; 2.B.166.236; 2.B.166.237; 2.B.166.238;
2.B.166.239; 2.B.166.154; 2.B.166.157; 2.B.166.166; 2.B.166.169; 2.B.166.172; 2.B.166.175;
30 2.B.166.240; 2.B.166.244; 2.B.169.228; 2.B.169.229; 2.B.169.230; 2.B.169.231; 2.B.169.236;
2.B.169.237; 2.B.169.238; 2.B.169.239; 2.B.169.154; 2.B.169.157; 2.B.169.166; 2.B.169.169;
2.B.169.172; 2.B.169.175; 2.B.169.240; 2.B.169.244; 2.B.172.228; 2.B.172.229; 2.B.172.230;
2.B.172.231; 2.B.172.236; 2.B.172.237; 2.B.172.238; 2.B.172.239; 2.B.172.154; 2.B.172.157;
2.B.172.166; 2.B.172.169; 2.B.172.172; 2.B.172.175; 2.B.172.240; 2.B.172.244; 2.B.175.228;
35 2.B.175.229; 2.B.175.230; 2.B.175.231; 2.B.175.236; 2.B.175.237; 2.B.175.238; 2.B.175.239;
2.B.175.154; 2.B.175.157; 2.B.175.166; 2.B.175.169; 2.B.175.172; 2.B.175.175; 2.B.175.240;
2.B.175.244; 2.B.240.228; 2.B.240.229; 2.B.240.230; 2.B.240.231; 2.B.240.236; 2.B.240.237;
2.B.240.238; 2.B.240.239; 2.B.240.154; 2.B.240.157; 2.B.240.166; 2.B.240.169; 2.B.240.172;
2.B.240.175; 2.B.240.240; 2.B.240.244; 2.B.244.228; 2.B.244.229; 2.B.244.230; 2.B.244.231;
40 2.B.244.236; 2.B.244.237; 2.B.244.238; 2.B.244.239; 2.B.244.154; 2.B.244.157; 2.B.244.166;
2.B.244.169; 2.B.244.172; 2.B.244.175; 2.B.244.240; 2.B.244.244;

Prodrugs of 2.D

- 45 2.D.228.228; 2.D.228.229; 2.D.228.230; 2.D.228.231; 2.D.228.236; 2.D.228.237;
2.D.228.238; 2.D.228.239; 2.D.228.154; 2.D.228.157; 2.D.228.166; 2.D.228.169;
2.D.228.172; 2.D.228.175; 2.D.228.240; 2.D.228.244; 2.D.229.228; 2.D.229.229;

2.D.229.230; 2.D.229.231; 2.D.229.236; 2.D.229.237; 2.D.229.238; 2.D.229.239;
 2.D.229.154; 2.D.229.157; 2.D.229.166; 2.D.229.169; 2.D.229.172; 2.D.229.175;
 2.D.229.240; 2.D.229.244; 2.D.230.228; 2.D.230.229; 2.D.230.230; 2.D.230.231;
 2.D.230.236; 2.D.230.237; 2.D.230.238; 2.D.230.239; 2.D.230.154; 2.D.230.157;
 5 2.D.230.166; 2.D.230.169; 2.D.230.172; 2.D.230.175; 2.D.230.240; 2.D.230.244;
 2.D.231.228; 2.D.231.229; 2.D.231.230; 2.D.231.231; 2.D.231.236; 2.D.231.237;
 2.D.231.238; 2.D.231.239; 2.D.231.154; 2.D.231.157; 2.D.231.166; 2.D.231.169;
 2.D.231.172; 2.D.231.175; 2.D.231.240; 2.D.231.244; 2.D.236.228; 2.D.236.229;
 2.D.236.230; 2.D.236.231; 2.D.236.236; 2.D.236.237; 2.D.236.238; 2.D.236.239;
 10 2.D.236.154; 2.D.236.157; 2.D.236.166; 2.D.236.169; 2.D.236.172; 2.D.236.175;
 2.D.236.240; 2.D.236.244; 2.D.237.228; 2.D.237.229; 2.D.237.230; 2.D.237.231;
 2.D.237.236; 2.D.237.237; 2.D.237.238; 2.D.237.239; 2.D.237.154; 2.D.237.157;
 2.D.237.166; 2.D.237.169; 2.D.237.172; 2.D.237.175; 2.D.237.240; 2.D.237.244;
 2.D.238.228; 2.D.238.229; 2.D.238.230; 2.D.238.231; 2.D.238.236; 2.D.238.237;
 15 2.D.238.238; 2.D.238.239; 2.D.238.154; 2.D.238.157; 2.D.238.166; 2.D.238.169;
 2.D.238.172; 2.D.238.175; 2.D.238.240; 2.D.238.244; 2.D.239.228; 2.D.239.229;
 2.D.239.230; 2.D.239.231; 2.D.239.236; 2.D.239.237; 2.D.239.238; 2.D.239.239;
 2.D.239.154; 2.D.239.157; 2.D.239.166; 2.D.239.169; 2.D.239.172; 2.D.239.175;
 2.D.239.240; 2.D.239.244; 2.D.154.228; 2.D.154.229; 2.D.154.230; 2.D.154.231;
 20 2.D.154.236; 2.D.154.237; 2.D.154.238; 2.D.154.239; 2.D.154.154; 2.D.154.157;
 2.D.154.166; 2.D.154.169; 2.D.154.172; 2.D.154.175; 2.D.154.240; 2.D.154.244;
 2.D.157.228; 2.D.157.229; 2.D.157.230; 2.D.157.231; 2.D.157.236; 2.D.157.237;
 2.D.157.238; 2.D.157.239; 2.D.157.154; 2.D.157.157; 2.D.157.166; 2.D.157.169;
 2.D.157.172; 2.D.157.175; 2.D.157.240; 2.D.157.244; 2.D.166.228; 2.D.166.229;
 25 2.D.166.230; 2.D.166.231; 2.D.166.236; 2.D.166.237; 2.D.166.238; 2.D.166.239;
 2.D.166.154; 2.D.166.157; 2.D.166.166; 2.D.166.169; 2.D.166.172; 2.D.166.175;
 2.D.166.240; 2.D.166.244; 2.D.169.228; 2.D.169.229; 2.D.169.230; 2.D.169.231;
 2.D.169.236; 2.D.169.237; 2.D.169.238; 2.D.169.239; 2.D.169.154; 2.D.169.157;
 2.D.169.166; 2.D.169.169; 2.D.169.172; 2.D.169.175; 2.D.169.240; 2.D.169.244;
 30 2.D.172.228; 2.D.172.229; 2.D.172.230; 2.D.172.231; 2.D.172.236; 2.D.172.237;
 2.D.172.238; 2.D.172.239; 2.D.172.154; 2.D.172.157; 2.D.172.166; 2.D.172.169;
 2.D.172.172; 2.D.172.175; 2.D.172.240; 2.D.172.244; 2.D.175.228; 2.D.175.229;
 2.D.175.230; 2.D.175.231; 2.D.175.236; 2.D.175.237; 2.D.175.238; 2.D.175.239;
 2.D.175.154; 2.D.175.157; 2.D.175.166; 2.D.175.169; 2.D.175.172; 2.D.175.175;
 35 2.D.175.240; 2.D.175.244; 2.D.240.228; 2.D.240.229; 2.D.240.230; 2.D.240.231;
 2.D.240.236; 2.D.240.237; 2.D.240.238; 2.D.240.239; 2.D.240.154; 2.D.240.157;
 2.D.240.166; 2.D.240.169; 2.D.240.172; 2.D.240.175; 2.D.240.240; 2.D.240.244;
 2.D.244.228; 2.D.244.229; 2.D.244.230; 2.D.244.231; 2.D.244.236; 2.D.244.237;
 2.D.244.238; 2.D.244.239; 2.D.244.154; 2.D.244.157; 2.D.244.166; 2.D.244.169;
 40 2.D.244.172; 2.D.244.175; 2.D.244.240; 2.D.244.244;

Prodrugs of 2.E

2.E.228.228; 2.E.228.229; 2.E.228.230; 2.E.228.231; 2.E.228.236; 2.E.228.237;
 2.E.228.238; 2.E.228.239; 2.E.228.154; 2.E.228.157; 2.E.228.166; 2.E.228.169; 2.E.228.172;
 45 2.E.228.175; 2.E.228.240; 2.E.228.244; 2.E.229.228; 2.E.229.229; 2.E.229.230; 2.E.229.231;
 2.E.229.236; 2.E.229.237; 2.E.229.238; 2.E.229.239; 2.E.229.154; 2.E.229.157; 2.E.229.166;

2.E.229.169; 2.E.229.172; 2.E.229.175; 2.E.229.240; 2.E.229.244; 2.E.230.228; 2.E.230.229;
 2.E.230.230; 2.E.230.231; 2.E.230.236; 2.E.230.237; 2.E.230.238; 2.E.230.239; 2.E.230.154;
 2.E.230.157; 2.E.230.166; 2.E.230.169; 2.E.230.172; 2.E.230.175; 2.E.230.240; 2.E.230.244;
 2.E.231.228; 2.E.231.229; 2.E.231.230; 2.E.231.231; 2.E.231.236; 2.E.231.237; 2.E.231.238;
 5 2.E.231.239; 2.E.231.154; 2.E.231.157; 2.E.231.166; 2.E.231.169; 2.E.231.172; 2.E.231.175;
 2.E.231.240; 2.E.231.244; 2.E.236.228; 2.E.236.229; 2.E.236.230; 2.E.236.231; 2.E.236.236;
 2.E.236.237; 2.E.236.238; 2.E.236.239; 2.E.236.154; 2.E.236.157; 2.E.236.166; 2.E.236.169;
 2.E.236.172; 2.E.236.175; 2.E.236.240; 2.E.236.244; 2.E.237.228; 2.E.237.229; 2.E.237.230;
 2.E.237.231; 2.E.237.236; 2.E.237.237; 2.E.237.238; 2.E.237.239; 2.E.237.154; 2.E.237.157;
 10 2.E.237.166; 2.E.237.169; 2.E.237.172; 2.E.237.175; 2.E.237.240; 2.E.237.244; 2.E.238.228;
 2.E.238.229; 2.E.238.230; 2.E.238.231; 2.E.238.236; 2.E.238.237; 2.E.238.238; 2.E.238.239;
 2.E.238.154; 2.E.238.157; 2.E.238.166; 2.E.238.169; 2.E.238.172; 2.E.238.175; 2.E.238.240;
 2.E.238.244; 2.E.239.228; 2.E.239.229; 2.E.239.230; 2.E.239.231; 2.E.239.236; 2.E.239.237;
 2.E.239.238; 2.E.239.239; 2.E.239.154; 2.E.239.157; 2.E.239.166; 2.E.239.169; 2.E.239.172;
 15 2.E.239.175; 2.E.239.240; 2.E.239.244; 2.E.154.228; 2.E.154.229; 2.E.154.230; 2.E.154.231;
 2.E.154.236; 2.E.154.237; 2.E.154.238; 2.E.154.239; 2.E.154.154; 2.E.154.157; 2.E.154.166;
 2.E.154.169; 2.E.154.172; 2.E.154.175; 2.E.154.240; 2.E.154.244; 2.E.157.228; 2.E.157.229;
 2.E.157.230; 2.E.157.231; 2.E.157.236; 2.E.157.237; 2.E.157.238; 2.E.157.239; 2.E.157.154;
 2.E.157.157; 2.E.157.166; 2.E.157.169; 2.E.157.172; 2.E.157.175; 2.E.157.240; 2.E.157.244;
 20 2.E.166.228; 2.E.166.229; 2.E.166.230; 2.E.166.231; 2.E.166.236; 2.E.166.237; 2.E.166.238;
 2.E.166.239; 2.E.166.154; 2.E.166.157; 2.E.166.166; 2.E.166.169; 2.E.166.172; 2.E.166.175;
 2.E.166.240; 2.E.166.244; 2.E.169.228; 2.E.169.229; 2.E.169.230; 2.E.169.231; 2.E.169.236;
 2.E.169.237; 2.E.169.238; 2.E.169.239; 2.E.169.154; 2.E.169.157; 2.E.169.166; 2.E.169.169;
 2.E.169.172; 2.E.169.175; 2.E.169.240; 2.E.169.244; 2.E.172.228; 2.E.172.229; 2.E.172.230;
 25 2.E.172.231; 2.E.172.236; 2.E.172.237; 2.E.172.238; 2.E.172.239; 2.E.172.154; 2.E.172.157;
 2.E.172.166; 2.E.172.169; 2.E.172.172; 2.E.172.175; 2.E.172.240; 2.E.172.244; 2.E.175.228;
 2.E.175.229; 2.E.175.230; 2.E.175.231; 2.E.175.236; 2.E.175.237; 2.E.175.238; 2.E.175.239;
 2.E.175.154; 2.E.175.157; 2.E.175.166; 2.E.175.169; 2.E.175.172; 2.E.175.175; 2.E.175.240;
 2.E.175.244; 2.E.240.228; 2.E.240.229; 2.E.240.230; 2.E.240.231; 2.E.240.236; 2.E.240.237;
 30 2.E.240.238; 2.E.240.239; 2.E.240.154; 2.E.240.157; 2.E.240.166; 2.E.240.169; 2.E.240.172;
 2.E.240.175; 2.E.240.240; 2.E.240.244; 2.E.244.228; 2.E.244.229; 2.E.244.230; 2.E.244.231;
 2.E.244.236; 2.E.244.237; 2.E.244.238; 2.E.244.239; 2.E.244.154; 2.E.244.157; 2.E.244.166;
 2.E.244.169; 2.E.244.172; 2.E.244.175; 2.E.244.240; 2.E.244.244;

35 Prodrugs of 2.G

2.G.228.228; 2.G.228.229; 2.G.228.230; 2.G.228.231; 2.G.228.236; 2.G.228.237;
 2.G.228.238; 2.G.228.239; 2.G.228.154; 2.G.228.157; 2.G.228.166; 2.G.228.169;
 2.G.228.172; 2.G.228.175; 2.G.228.240; 2.G.228.244; 2.G.229.228; 2.G.229.229;
 2.G.229.230; 2.G.229.231; 2.G.229.236; 2.G.229.237; 2.G.229.238; 2.G.229.239;
 40 2.G.229.154; 2.G.229.157; 2.G.229.166; 2.G.229.169; 2.G.229.172; 2.G.229.175;
 2.G.229.240; 2.G.229.244; 2.G.230.228; 2.G.230.229; 2.G.230.230; 2.G.230.231;
 2.G.230.236; 2.G.230.237; 2.G.230.238; 2.G.230.239; 2.G.230.154; 2.G.230.157;
 2.G.230.166; 2.G.230.169; 2.G.230.172; 2.G.230.175; 2.G.230.240; 2.G.230.244;
 2.G.231.228; 2.G.231.229; 2.G.231.230; 2.G.231.231; 2.G.231.236; 2.G.231.237;
 45 2.G.231.238; 2.G.231.239; 2.G.231.154; 2.G.231.157; 2.G.231.166; 2.G.231.169;
 2.G.231.172; 2.G.231.175; 2.G.231.240; 2.G.231.244; 2.G.236.228; 2.G.236.229;

- 2.G.236.230; 2.G.236.231; 2.G.236.236; 2.G.236.237; 2.G.236.238; 2.G.236.239;
 2.G.236.154; 2.G.236.157; 2.G.236.166; 2.G.236.169; 2.G.236.172; 2.G.236.175;
 2.G.236.240; 2.G.236.244; 2.G.237.228; 2.G.237.229; 2.G.237.230; 2.G.237.231;
 2.G.237.236; 2.G.237.237; 2.G.237.238; 2.G.237.239; 2.G.237.154; 2.G.237.157;
 5 2.G.237.166; 2.G.237.169; 2.G.237.172; 2.G.237.175; 2.G.237.240; 2.G.237.244;
 2.G.238.228; 2.G.238.229; 2.G.238.230; 2.G.238.231; 2.G.238.236; 2.G.238.237;
 2.G.238.238; 2.G.238.239; 2.G.238.154; 2.G.238.157; 2.G.238.166; 2.G.238.169;
 2.G.238.172; 2.G.238.175; 2.G.238.240; 2.G.238.244; 2.G.239.228; 2.G.239.229;
 2.G.239.230; 2.G.239.231; 2.G.239.236; 2.G.239.237; 2.G.239.238; 2.G.239.239;
 10 2.G.239.154; 2.G.239.157; 2.G.239.166; 2.G.239.169; 2.G.239.172; 2.G.239.175;
 2.G.239.240; 2.G.239.244; 2.G.154.228; 2.G.154.229; 2.G.154.230; 2.G.154.231;
 2.G.154.236; 2.G.154.237; 2.G.154.238; 2.G.154.239; 2.G.154.154; 2.G.154.157;
 2.G.154.166; 2.G.154.169; 2.G.154.172; 2.G.154.175; 2.G.154.240; 2.G.154.244;
 2.G.157.228; 2.G.157.229; 2.G.157.230; 2.G.157.231; 2.G.157.236; 2.G.157.237;
 15 2.G.157.238; 2.G.157.239; 2.G.157.154; 2.G.157.157; 2.G.157.166; 2.G.157.169;
 2.G.157.172; 2.G.157.175; 2.G.157.240; 2.G.157.244; 2.G.166.228; 2.G.166.229;
 2.G.166.230; 2.G.166.231; 2.G.166.236; 2.G.166.237; 2.G.166.238; 2.G.166.239;
 2.G.166.154; 2.G.166.157; 2.G.166.166; 2.G.166.169; 2.G.166.172; 2.G.166.175;
 2.G.166.240; 2.G.166.244; 2.G.169.228; 2.G.169.229; 2.G.169.230; 2.G.169.231;
 20 2.G.169.236; 2.G.169.237; 2.G.169.238; 2.G.169.239; 2.G.169.154; 2.G.169.157;
 2.G.169.166; 2.G.169.169; 2.G.169.172; 2.G.169.175; 2.G.169.240; 2.G.169.244;
 2.G.172.228; 2.G.172.229; 2.G.172.230; 2.G.172.231; 2.G.172.236; 2.G.172.237;
 2.G.172.238; 2.G.172.239; 2.G.172.154; 2.G.172.157; 2.G.172.166; 2.G.172.169;
 2.G.172.172; 2.G.172.175; 2.G.172.240; 2.G.172.244; 2.G.175.228; 2.G.175.229;
 25 2.G.175.230; 2.G.175.231; 2.G.175.236; 2.G.175.237; 2.G.175.238; 2.G.175.239;
 2.G.175.154; 2.G.175.157; 2.G.175.166; 2.G.175.169; 2.G.175.172; 2.G.175.175;
 2.G.175.240; 2.G.175.244; 2.G.240.228; 2.G.240.229; 2.G.240.230; 2.G.240.231;
 2.G.240.236; 2.G.240.237; 2.G.240.238; 2.G.240.239; 2.G.240.154; 2.G.240.157;
 2.G.240.166; 2.G.240.169; 2.G.240.172; 2.G.240.175; 2.G.240.240; 2.G.240.244;
 30 2.G.244.228; 2.G.244.229; 2.G.244.230; 2.G.244.231; 2.G.244.236; 2.G.244.237;
 2.G.244.238; 2.G.244.239; 2.G.244.154; 2.G.244.157; 2.G.244.166; 2.G.244.169;
 2.G.244.172; 2.G.244.175; 2.G.244.240; 2.G.244.244;

Prodrugs of 2.I

- 35 2.I.228.228; 2.I.228.229; 2.I.228.230; 2.I.228.231; 2.I.228.236; 2.I.228.237; 2.I.228.238;
 2.I.228.239; 2.I.228.154; 2.I.228.157; 2.I.228.166; 2.I.228.169; 2.I.228.172; 2.I.228.175;
 2.I.228.240; 2.I.228.244; 2.I.229.228; 2.I.229.229; 2.I.229.230; 2.I.229.231; 2.I.229.236;
 2.I.229.237; 2.I.229.238; 2.I.229.239; 2.I.229.154; 2.I.229.157; 2.I.229.166; 2.I.229.169;
 2.I.229.172; 2.I.229.175; 2.I.229.240; 2.I.229.244; 2.I.230.228; 2.I.230.229; 2.I.230.230;
 40 2.I.230.231; 2.I.230.236; 2.I.230.237; 2.I.230.238; 2.I.230.239; 2.I.230.154; 2.I.230.157;
 2.I.230.166; 2.I.230.169; 2.I.230.172; 2.I.230.175; 2.I.230.240; 2.I.230.244; 2.I.231.228;
 2.I.231.229; 2.I.231.230; 2.I.231.231; 2.I.231.236; 2.I.231.237; 2.I.231.238; 2.I.231.239;
 2.I.231.154; 2.I.231.157; 2.I.231.166; 2.I.231.169; 2.I.231.172; 2.I.231.175; 2.I.231.240;
 2.I.231.244; 2.I.236.228; 2.I.236.229; 2.I.236.230; 2.I.236.231; 2.I.236.236; 2.I.236.237;
 45 2.I.236.238; 2.I.236.239; 2.I.236.154; 2.I.236.157; 2.I.236.166; 2.I.236.169; 2.I.236.172;
 2.I.236.175; 2.I.236.240; 2.I.236.244; 2.I.237.228; 2.I.237.229; 2.I.237.230; 2.I.237.231;

2.I.237.236; 2.I.237.237; 2.I.237.238; 2.I.237.239; 2.I.237.154; 2.I.237.157; 2.I.237.166;
 2.I.237.169; 2.I.237.172; 2.I.237.175; 2.I.237.240; 2.I.237.244; 2.I.238.228; 2.I.238.229;
 2.I.238.230; 2.I.238.231; 2.I.238.236; 2.I.238.237; 2.I.238.238; 2.I.238.239; 2.I.238.154;
 2.I.238.157; 2.I.238.166; 2.I.238.169; 2.I.238.172; 2.I.238.175; 2.I.238.240; 2.I.238.244;
 5 2.I.239.228; 2.I.239.229; 2.I.239.230; 2.I.239.231; 2.I.239.236; 2.I.239.237; 2.I.239.238;
 2.I.239.239; 2.I.239.154; 2.I.239.157; 2.I.239.166; 2.I.239.169; 2.I.239.172; 2.I.239.175;
 2.I.239.240; 2.I.239.244; 2.I.154.228; 2.I.154.229; 2.I.154.230; 2.I.154.231; 2.I.154.236;
 2.I.154.237; 2.I.154.238; 2.I.154.239; 2.I.154.154; 2.I.154.157; 2.I.154.166; 2.I.154.169;
 2.I.154.172; 2.I.154.175; 2.I.154.240; 2.I.154.244; 2.I.157.228; 2.I.157.229; 2.I.157.230;
 10 2.I.157.231; 2.I.157.236; 2.I.157.237; 2.I.157.238; 2.I.157.239; 2.I.157.154; 2.I.157.157;
 2.I.157.166; 2.I.157.169; 2.I.157.172; 2.I.157.175; 2.I.157.240; 2.I.157.244; 2.I.166.228;
 2.I.166.229; 2.I.166.230; 2.I.166.231; 2.I.166.236; 2.I.166.237; 2.I.166.238; 2.I.166.239;
 2.I.166.154; 2.I.166.157; 2.I.166.166; 2.I.166.169; 2.I.166.172; 2.I.166.175; 2.I.166.240;
 2.I.166.244; 2.I.169.228; 2.I.169.229; 2.I.169.230; 2.I.169.231; 2.I.169.236; 2.I.169.237;
 15 2.I.169.238; 2.I.169.239; 2.I.169.154; 2.I.169.157; 2.I.169.166; 2.I.169.169; 2.I.169.172;
 2.I.169.175; 2.I.169.240; 2.I.169.244; 2.I.172.228; 2.I.172.229; 2.I.172.230; 2.I.172.231;
 2.I.172.236; 2.I.172.237; 2.I.172.238; 2.I.172.239; 2.I.172.154; 2.I.172.157; 2.I.172.166;
 2.I.172.169; 2.I.172.172; 2.I.172.175; 2.I.172.240; 2.I.172.244; 2.I.175.228; 2.I.175.229;
 2.I.175.230; 2.I.175.231; 2.I.175.236; 2.I.175.237; 2.I.175.238; 2.I.175.239; 2.I.175.154;
 20 2.I.175.157; 2.I.175.166; 2.I.175.169; 2.I.175.172; 2.I.175.175; 2.I.175.240; 2.I.175.244;
 2.I.240.228; 2.I.240.229; 2.I.240.230; 2.I.240.231; 2.I.240.236; 2.I.240.237; 2.I.240.238;
 2.I.240.239; 2.I.240.154; 2.I.240.157; 2.I.240.166; 2.I.240.169; 2.I.240.172; 2.I.240.175;
 2.I.240.240; 2.I.240.244; 2.I.244.228; 2.I.244.229; 2.I.244.230; 2.I.244.231; 2.I.244.236;
 2.I.244.237; 2.I.244.238; 2.I.244.239; 2.I.244.154; 2.I.244.157; 2.I.244.166; 2.I.244.169;
 25 2.I.244.172; 2.I.244.175; 2.I.244.240; 2.I.244.244;

Prodrugs of 2.I

2.J.228.228; 2.J.228.229; 2.J.228.230; 2.J.228.231; 2.J.228.236; 2.J.228.237; 2.J.228.238;
 2.J.228.239; 2.J.228.154; 2.J.228.157; 2.J.228.166; 2.J.228.169; 2.J.228.172; 2.J.228.175;
 30 2.J.228.240; 2.J.228.244; 2.J.229.228; 2.J.229.229; 2.J.229.230; 2.J.229.231; 2.J.229.236;
 2.J.229.237; 2.J.229.238; 2.J.229.239; 2.J.229.154; 2.J.229.157; 2.J.229.166; 2.J.229.169;
 2.J.229.172; 2.J.229.175; 2.J.229.240; 2.J.229.244; 2.J.230.228; 2.J.230.229; 2.J.230.230;
 2.J.230.231; 2.J.230.236; 2.J.230.237; 2.J.230.238; 2.J.230.239; 2.J.230.154; 2.J.230.157;
 2.J.230.166; 2.J.230.169; 2.J.230.172; 2.J.230.175; 2.J.230.240; 2.J.230.244; 2.J.231.228;
 35 2.J.231.229; 2.J.231.230; 2.J.231.231; 2.J.231.236; 2.J.231.237; 2.J.231.238; 2.J.231.239;
 2.J.231.154; 2.J.231.157; 2.J.231.166; 2.J.231.169; 2.J.231.172; 2.J.231.175; 2.J.231.240;
 2.J.231.244; 2.J.236.228; 2.J.236.229; 2.J.236.230; 2.J.236.231; 2.J.236.236; 2.J.236.237;
 2.J.236.238; 2.J.236.239; 2.J.236.154; 2.J.236.157; 2.J.236.166; 2.J.236.169; 2.J.236.172;
 2.J.236.175; 2.J.236.240; 2.J.236.244; 2.J.237.228; 2.J.237.229; 2.J.237.230; 2.J.237.231;
 40 2.J.237.236; 2.J.237.237; 2.J.237.238; 2.J.237.239; 2.J.237.154; 2.J.237.157; 2.J.237.166;
 2.J.237.169; 2.J.237.172; 2.J.237.175; 2.J.237.240; 2.J.237.244; 2.J.238.228; 2.J.238.229;
 2.J.238.230; 2.J.238.231; 2.J.238.236; 2.J.238.237; 2.J.238.238; 2.J.238.239; 2.J.238.154;
 2.J.238.157; 2.J.238.166; 2.J.238.169; 2.J.238.172; 2.J.238.175; 2.J.238.240; 2.J.238.244;
 2.J.239.228; 2.J.239.229; 2.J.239.230; 2.J.239.231; 2.J.239.236; 2.J.239.237; 2.J.239.238;
 45 2.J.239.239; 2.J.239.154; 2.J.239.157; 2.J.239.166; 2.J.239.169; 2.J.239.172; 2.J.239.175;
 2.J.239.240; 2.J.239.244; 2.J.154.228; 2.J.154.229; 2.J.154.230; 2.J.154.231; 2.J.154.236;

- 2.J.154.237; 2.J.154.238; 2.J.154.239; 2.J.154.154; 2.J.154.157; 2.J.154.166; 2.J.154.169;
 2.J.154.172; 2.J.154.175; 2.J.154.240; 2.J.154.244; 2.J.157.228; 2.J.157.229; 2.J.157.230;
 2.J.157.231; 2.J.157.236; 2.J.157.237; 2.J.157.238; 2.J.157.239; 2.J.157.154; 2.J.157.157;
 2.J.157.166; 2.J.157.169; 2.J.157.172; 2.J.157.175; 2.J.157.240; 2.J.157.244; 2.J.166.228;
 5 2.J.166.229; 2.J.166.230; 2.J.166.231; 2.J.166.236; 2.J.166.237; 2.J.166.238; 2.J.166.239;
 2.J.166.154; 2.J.166.157; 2.J.166.166; 2.J.166.169; 2.J.166.172; 2.J.166.175; 2.J.166.240;
 2.J.166.244; 2.J.169.228; 2.J.169.229; 2.J.169.230; 2.J.169.231; 2.J.169.236; 2.J.169.237;
 2.J.169.238; 2.J.169.239; 2.J.169.154; 2.J.169.157; 2.J.169.166; 2.J.169.169; 2.J.169.172;
 2.J.169.175; 2.J.169.240; 2.J.169.244; 2.J.172.228; 2.J.172.229; 2.J.172.230; 2.J.172.231;
 10 2.J.172.236; 2.J.172.237; 2.J.172.238; 2.J.172.239; 2.J.172.154; 2.J.172.157; 2.J.172.166;
 2.J.172.169; 2.J.172.172; 2.J.172.175; 2.J.172.240; 2.J.172.244; 2.J.175.228; 2.J.175.229;
 2.J.175.230; 2.J.175.231; 2.J.175.236; 2.J.175.237; 2.J.175.238; 2.J.175.239; 2.J.175.154;
 2.J.175.157; 2.J.175.166; 2.J.175.169; 2.J.175.172; 2.J.175.175; 2.J.175.240; 2.J.175.244;
 2.J.240.228; 2.J.240.229; 2.J.240.230; 2.J.240.231; 2.J.240.236; 2.J.240.237; 2.J.240.238;
 15 2.J.240.239; 2.J.240.154; 2.J.240.157; 2.J.240.166; 2.J.240.169; 2.J.240.172; 2.J.240.175;
 2.J.240.240; 2.J.240.244; 2.J.244.228; 2.J.244.229; 2.J.244.230; 2.J.244.231; 2.J.244.236;
 2.J.244.237; 2.J.244.238; 2.J.244.239; 2.J.244.154; 2.J.244.157; 2.J.244.166; 2.J.244.169;
 2.J.244.172; 2.J.244.175; 2.J.244.240; 2.J.244.244;
- 20 Prodrugs of 2.L
 2.L.228.228; 2.L.228.229; 2.L.228.230; 2.L.228.231; 2.L.228.236; 2.L.228.237;
 2.L.228.238; 2.L.228.239; 2.L.228.154; 2.L.228.157; 2.L.228.166; 2.L.228.169; 2.L.228.172;
 2.L.228.175; 2.L.228.240; 2.L.228.244; 2.L.229.228; 2.L.229.229; 2.L.229.230; 2.L.229.231;
 2.L.229.236; 2.L.229.237; 2.L.229.238; 2.L.229.239; 2.L.229.154; 2.L.229.157; 2.L.229.166;
 25 2.L.229.169; 2.L.229.172; 2.L.229.175; 2.L.229.240; 2.L.229.244; 2.L.230.228; 2.L.230.229;
 2.L.230.230; 2.L.230.231; 2.L.230.236; 2.L.230.237; 2.L.230.238; 2.L.230.239; 2.L.230.154;
 2.L.230.157; 2.L.230.166; 2.L.230.169; 2.L.230.172; 2.L.230.175; 2.L.230.240; 2.L.230.244;
 2.L.231.228; 2.L.231.229; 2.L.231.230; 2.L.231.231; 2.L.231.236; 2.L.231.237; 2.L.231.238;
 2.L.231.239; 2.L.231.154; 2.L.231.157; 2.L.231.166; 2.L.231.169; 2.L.231.172; 2.L.231.175;
 30 2.L.231.240; 2.L.231.244; 2.L.236.228; 2.L.236.229; 2.L.236.230; 2.L.236.231; 2.L.236.236;
 2.L.236.237; 2.L.236.238; 2.L.236.239; 2.L.236.154; 2.L.236.157; 2.L.236.166; 2.L.236.169;
 2.L.236.172; 2.L.236.175; 2.L.236.240; 2.L.236.244; 2.L.237.228; 2.L.237.229; 2.L.237.230;
 2.L.237.231; 2.L.237.236; 2.L.237.237; 2.L.237.238; 2.L.237.239; 2.L.237.154; 2.L.237.157;
 2.L.237.166; 2.L.237.169; 2.L.237.172; 2.L.237.175; 2.L.237.240; 2.L.237.244; 2.L.238.228;
 35 2.L.238.229; 2.L.238.230; 2.L.238.231; 2.L.238.236; 2.L.238.237; 2.L.238.238; 2.L.238.239;
 2.L.238.154; 2.L.238.157; 2.L.238.166; 2.L.238.169; 2.L.238.172; 2.L.238.175; 2.L.238.240;
 2.L.238.244; 2.L.239.228; 2.L.239.229; 2.L.239.230; 2.L.239.231; 2.L.239.236; 2.L.239.237;
 2.L.239.238; 2.L.239.239; 2.L.239.154; 2.L.239.157; 2.L.239.166; 2.L.239.169; 2.L.239.172;
 2.L.239.175; 2.L.239.240; 2.L.239.244; 2.L.154.228; 2.L.154.229; 2.L.154.230; 2.L.154.231;
 40 2.L.154.236; 2.L.154.237; 2.L.154.238; 2.L.154.239; 2.L.154.154; 2.L.154.157; 2.L.154.166;
 2.L.154.169; 2.L.154.172; 2.L.154.175; 2.L.154.240; 2.L.154.244; 2.L.157.228; 2.L.157.229;
 2.L.157.230; 2.L.157.231; 2.L.157.236; 2.L.157.237; 2.L.157.238; 2.L.157.239; 2.L.157.154;
 2.L.157.157; 2.L.157.166; 2.L.157.169; 2.L.157.172; 2.L.157.175; 2.L.157.240; 2.L.157.244;
 2.L.166.228; 2.L.166.229; 2.L.166.230; 2.L.166.231; 2.L.166.236; 2.L.166.237; 2.L.166.238;
 45 2.L.166.239; 2.L.166.154; 2.L.166.157; 2.L.166.166; 2.L.166.169; 2.L.166.172; 2.L.166.175;
 2.L.166.240; 2.L.166.244; 2.L.169.228; 2.L.169.229; 2.L.169.230; 2.L.169.231; 2.L.169.236;

2.L.169.237; 2.L.169.238; 2.L.169.239; 2.L.169.154; 2.L.169.157; 2.L.169.166; 2.L.169.169;
 2.L.169.172; 2.L.169.175; 2.L.169.240; 2.L.169.244; 2.L.172.228; 2.L.172.229; 2.L.172.230;
 2.L.172.231; 2.L.172.236; 2.L.172.237; 2.L.172.238; 2.L.172.239; 2.L.172.154; 2.L.172.157;
 2.L.172.166; 2.L.172.169; 2.L.172.172; 2.L.172.175; 2.L.172.240; 2.L.172.244; 2.L.175.228;
 5 2.L.175.229; 2.L.175.230; 2.L.175.231; 2.L.175.236; 2.L.175.237; 2.L.175.238; 2.L.175.239;
 2.L.175.154; 2.L.175.157; 2.L.175.166; 2.L.175.169; 2.L.175.172; 2.L.175.175; 2.L.175.240;
 2.L.175.244; 2.L.240.228; 2.L.240.229; 2.L.240.230; 2.L.240.231; 2.L.240.236; 2.L.240.237;
 2.L.240.238; 2.L.240.239; 2.L.240.154; 2.L.240.157; 2.L.240.166; 2.L.240.169; 2.L.240.172;
 2.L.240.175; 2.L.240.240; 2.L.240.244; 2.L.244.228; 2.L.244.229; 2.L.244.230; 2.L.244.231;
 10 2.L.244.236; 2.L.244.237; 2.L.244.238; 2.L.244.239; 2.L.244.154; 2.L.244.157; 2.L.244.166;
 2.L.244.169; 2.L.244.172; 2.L.244.175; 2.L.244.240; 2.L.244.244;

Prodrugs of 2.O

2.O.228.228; 2.O.228.229; 2.O.228.230; 2.O.228.231; 2.O.228.236; 2.O.228.237;
 15 2.O.228.238; 2.O.228.239; 2.O.228.154; 2.O.228.157; 2.O.228.166; 2.O.228.169;
 2.O.228.172; 2.O.228.175; 2.O.228.240; 2.O.228.244; 2.O.229.228; 2.O.229.229;
 2.O.229.230; 2.O.229.231; 2.O.229.236; 2.O.229.237; 2.O.229.238; 2.O.229.239;
 2.O.229.154; 2.O.229.157; 2.O.229.166; 2.O.229.169; 2.O.229.172; 2.O.229.175;
 2.O.229.240; 2.O.229.244; 2.O.230.228; 2.O.230.229; 2.O.230.230; 2.O.230.231;
 20 2.O.230.236; 2.O.230.237; 2.O.230.238; 2.O.230.239; 2.O.230.154; 2.O.230.157;
 2.O.230.166; 2.O.230.169; 2.O.230.172; 2.O.230.175; 2.O.230.240; 2.O.230.244;
 2.O.231.228; 2.O.231.229; 2.O.231.230; 2.O.231.231; 2.O.231.236; 2.O.231.237;
 2.O.231.238; 2.O.231.239; 2.O.231.154; 2.O.231.157; 2.O.231.166; 2.O.231.169;
 2.O.231.172; 2.O.231.175; 2.O.231.240; 2.O.231.244; 2.O.236.228; 2.O.236.229;
 25 2.O.236.230; 2.O.236.231; 2.O.236.236; 2.O.236.237; 2.O.236.238; 2.O.236.239;
 2.O.236.154; 2.O.236.157; 2.O.236.166; 2.O.236.169; 2.O.236.172; 2.O.236.175;
 2.O.236.240; 2.O.236.244; 2.O.237.228; 2.O.237.229; 2.O.237.230; 2.O.237.231;
 2.O.237.236; 2.O.237.237; 2.O.237.238; 2.O.237.239; 2.O.237.154; 2.O.237.157;
 2.O.237.166; 2.O.237.169; 2.O.237.172; 2.O.237.175; 2.O.237.240; 2.O.237.244;
 30 2.O.238.228; 2.O.238.229; 2.O.238.230; 2.O.238.231; 2.O.238.236; 2.O.238.237;
 2.O.238.238; 2.O.238.239; 2.O.238.154; 2.O.238.157; 2.O.238.166; 2.O.238.169;
 2.O.238.172; 2.O.238.175; 2.O.238.240; 2.O.238.244; 2.O.239.228; 2.O.239.229;
 2.O.239.230; 2.O.239.231; 2.O.239.236; 2.O.239.237; 2.O.239.238; 2.O.239.239;
 2.O.239.154; 2.O.239.157; 2.O.239.166; 2.O.239.169; 2.O.239.172; 2.O.239.175;
 35 2.O.239.240; 2.O.239.244; 2.O.154.228; 2.O.154.229; 2.O.154.230; 2.O.154.231;
 2.O.154.236; 2.O.154.237; 2.O.154.238; 2.O.154.239; 2.O.154.154; 2.O.154.157;
 2.O.154.166; 2.O.154.169; 2.O.154.172; 2.O.154.175; 2.O.154.240; 2.O.154.244;
 2.O.157.228; 2.O.157.229; 2.O.157.230; 2.O.157.231; 2.O.157.236; 2.O.157.237;
 2.O.157.238; 2.O.157.239; 2.O.157.154; 2.O.157.157; 2.O.157.166; 2.O.157.169;
 40 2.O.157.172; 2.O.157.175; 2.O.157.240; 2.O.157.244; 2.O.166.228; 2.O.166.229;
 2.O.166.230; 2.O.166.231; 2.O.166.236; 2.O.166.237; 2.O.166.238; 2.O.166.239;
 2.O.166.154; 2.O.166.157; 2.O.166.166; 2.O.166.169; 2.O.166.172; 2.O.166.175;
 2.O.166.240; 2.O.166.244; 2.O.169.228; 2.O.169.229; 2.O.169.230; 2.O.169.231;
 2.O.169.236; 2.O.169.237; 2.O.169.238; 2.O.169.239; 2.O.169.154; 2.O.169.157;
 45 2.O.169.166; 2.O.169.169; 2.O.169.172; 2.O.169.175; 2.O.169.240; 2.O.169.244;
 2.O.172.228; 2.O.172.229; 2.O.172.230; 2.O.172.231; 2.O.172.236; 2.O.172.237;

2.O.172.238; 2.O.172.239; 2.O.172.154; 2.O.172.157; 2.O.172.166; 2.O.172.169;
 2.O.172.172; 2.O.172.175; 2.O.172.240; 2.O.172.244; 2.O.175.228; 2.O.175.229;
 2.O.175.230; 2.O.175.231; 2.O.175.236; 2.O.175.237; 2.O.175.238; 2.O.175.239;
 2.O.175.154; 2.O.175.157; 2.O.175.166; 2.O.175.169; 2.O.175.172; 2.O.175.175;
 5 2.O.175.240; 2.O.175.244; 2.O.240.228; 2.O.240.229; 2.O.240.230; 2.O.240.231;
 2.O.240.236; 2.O.240.237; 2.O.240.238; 2.O.240.239; 2.O.240.154; 2.O.240.157;
 2.O.240.166; 2.O.240.169; 2.O.240.172; 2.O.240.175; 2.O.240.240; 2.O.240.244;
 2.O.244.228; 2.O.244.229; 2.O.244.230; 2.O.244.231; 2.O.244.236; 2.O.244.237;
 2.O.244.238; 2.O.244.239; 2.O.244.154; 2.O.244.157; 2.O.244.166; 2.O.244.169;
 10 2.O.244.172; 2.O.244.175; 2.O.244.240; 2.O.244.244;

Prodrugs of 2.P

2.P.228.228; 2.P.228.229; 2.P.228.230; 2.P.228.231; 2.P.228.236; 2.P.228.237;
 2.P.228.238; 2.P.228.239; 2.P.228.154; 2.P.228.157; 2.P.228.166; 2.P.228.169; 2.P.228.172;
 15 2.P.228.175; 2.P.228.240; 2.P.228.244; 2.P.229.228; 2.P.229.229; 2.P.229.230; 2.P.229.231;
 2.P.229.236; 2.P.229.237; 2.P.229.238; 2.P.229.239; 2.P.229.154; 2.P.229.157; 2.P.229.166;
 2.P.229.169; 2.P.229.172; 2.P.229.175; 2.P.229.240; 2.P.229.244; 2.P.230.228; 2.P.230.229;
 2.P.230.230; 2.P.230.231; 2.P.230.236; 2.P.230.237; 2.P.230.238; 2.P.230.239; 2.P.230.154;
 2.P.230.157; 2.P.230.166; 2.P.230.169; 2.P.230.172; 2.P.230.175; 2.P.230.240; 2.P.230.244;
 20 2.P.231.228; 2.P.231.229; 2.P.231.230; 2.P.231.231; 2.P.231.236; 2.P.231.237; 2.P.231.238;
 2.P.231.239; 2.P.231.154; 2.P.231.157; 2.P.231.166; 2.P.231.169; 2.P.231.172; 2.P.231.175;
 2.P.231.240; 2.P.231.244; 2.P.236.228; 2.P.236.229; 2.P.236.230; 2.P.236.231; 2.P.236.236;
 2.P.236.237; 2.P.236.238; 2.P.236.239; 2.P.236.154; 2.P.236.157; 2.P.236.166; 2.P.236.169;
 2.P.236.172; 2.P.236.175; 2.P.236.240; 2.P.236.244; 2.P.237.228; 2.P.237.229; 2.P.237.230;
 25 2.P.237.231; 2.P.237.236; 2.P.237.237; 2.P.237.238; 2.P.237.239; 2.P.237.154; 2.P.237.157;
 2.P.237.166; 2.P.237.169; 2.P.237.172; 2.P.237.175; 2.P.237.240; 2.P.237.244; 2.P.238.228;
 2.P.238.229; 2.P.238.230; 2.P.238.231; 2.P.238.236; 2.P.238.237; 2.P.238.238; 2.P.238.239;
 2.P.238.154; 2.P.238.157; 2.P.238.166; 2.P.238.169; 2.P.238.172; 2.P.238.175; 2.P.238.240;
 2.P.238.244; 2.P.239.228; 2.P.239.229; 2.P.239.230; 2.P.239.231; 2.P.239.236; 2.P.239.237;
 30 2.P.239.238; 2.P.239.239; 2.P.239.154; 2.P.239.157; 2.P.239.166; 2.P.239.169; 2.P.239.172;
 2.P.239.175; 2.P.239.240; 2.P.239.244; 2.P.154.228; 2.P.154.229; 2.P.154.230; 2.P.154.231;
 2.P.154.236; 2.P.154.237; 2.P.154.238; 2.P.154.239; 2.P.154.154; 2.P.154.157; 2.P.154.166;
 2.P.154.169; 2.P.154.172; 2.P.154.175; 2.P.154.240; 2.P.154.244; 2.P.157.228; 2.P.157.229;
 2.P.157.230; 2.P.157.231; 2.P.157.236; 2.P.157.237; 2.P.157.238; 2.P.157.239; 2.P.157.154;
 35 2.P.157.157; 2.P.157.166; 2.P.157.169; 2.P.157.172; 2.P.157.175; 2.P.157.240; 2.P.157.244;
 2.P.166.228; 2.P.166.229; 2.P.166.230; 2.P.166.231; 2.P.166.236; 2.P.166.237; 2.P.166.238;
 2.P.166.239; 2.P.166.154; 2.P.166.157; 2.P.166.166; 2.P.166.169; 2.P.166.172; 2.P.166.175;
 2.P.166.240; 2.P.166.244; 2.P.169.228; 2.P.169.229; 2.P.169.230; 2.P.169.231; 2.P.169.236;
 2.P.169.237; 2.P.169.238; 2.P.169.239; 2.P.169.154; 2.P.169.157; 2.P.169.166; 2.P.169.169;
 40 2.P.169.172; 2.P.169.175; 2.P.169.240; 2.P.169.244; 2.P.172.228; 2.P.172.229; 2.P.172.230;
 2.P.172.231; 2.P.172.236; 2.P.172.237; 2.P.172.238; 2.P.172.239; 2.P.172.154; 2.P.172.157;
 2.P.172.166; 2.P.172.169; 2.P.172.172; 2.P.172.175; 2.P.172.240; 2.P.172.244; 2.P.175.228;
 2.P.175.229; 2.P.175.230; 2.P.175.231; 2.P.175.236; 2.P.175.237; 2.P.175.238; 2.P.175.239;
 2.P.175.154; 2.P.175.157; 2.P.175.166; 2.P.175.169; 2.P.175.172; 2.P.175.175; 2.P.175.240;
 45 2.P.175.244; 2.P.240.228; 2.P.240.229; 2.P.240.230; 2.P.240.231; 2.P.240.236; 2.P.240.237;
 2.P.240.238; 2.P.240.239; 2.P.240.154; 2.P.240.157; 2.P.240.166; 2.P.240.169; 2.P.240.172;

2.P.240.175; 2.P.240.240; 2.P.240.244; 2.P.244.228; 2.P.244.229; 2.P.244.230; 2.P.244.231;
 2.P.244.236; 2.P.244.237; 2.P.244.238; 2.P.244.239; 2.P.244.154; 2.P.244.157; 2.P.244.166;
 2.P.244.169; 2.P.244.172; 2.P.244.175; 2.P.244.240; 2.P.244.244;

5 Prodrugs of 2.U

2.U.228.228; 2.U.228.229; 2.U.228.230; 2.U.228.231; 2.U.228.236; 2.U.228.237;
 2.U.228.238; 2.U.228.239; 2.U.228.154; 2.U.228.157; 2.U.228.166; 2.U.228.169;
 2.U.228.172; 2.U.228.175; 2.U.228.240; 2.U.228.244; 2.U.229.228; 2.U.229.229;
 2.U.229.230; 2.U.229.231; 2.U.229.236; 2.U.229.237; 2.U.229.238; 2.U.229.239;
 10 2.U.229.154; 2.U.229.157; 2.U.229.166; 2.U.229.169; 2.U.229.172; 2.U.229.175;
 2.U.229.240; 2.U.229.244; 2.U.230.228; 2.U.230.229; 2.U.230.230; 2.U.230.231;
 2.U.230.236; 2.U.230.237; 2.U.230.238; 2.U.230.239; 2.U.230.154; 2.U.230.157;
 2.U.230.166; 2.U.230.169; 2.U.230.172; 2.U.230.175; 2.U.230.240; 2.U.230.244;
 2.U.231.228; 2.U.231.229; 2.U.231.230; 2.U.231.231; 2.U.231.236; 2.U.231.237;
 15 2.U.231.238; 2.U.231.239; 2.U.231.154; 2.U.231.157; 2.U.231.166; 2.U.231.169;
 2.U.231.172; 2.U.231.175; 2.U.231.240; 2.U.231.244; 2.U.236.228; 2.U.236.229;
 2.U.236.230; 2.U.236.231; 2.U.236.236; 2.U.236.237; 2.U.236.238; 2.U.236.239;
 2.U.236.154; 2.U.236.157; 2.U.236.166; 2.U.236.169; 2.U.236.172; 2.U.236.175;
 2.U.236.240; 2.U.236.244; 2.U.237.228; 2.U.237.229; 2.U.237.230; 2.U.237.231;
 20 2.U.237.236; 2.U.237.237; 2.U.237.238; 2.U.237.239; 2.U.237.154; 2.U.237.157;
 2.U.237.166; 2.U.237.169; 2.U.237.172; 2.U.237.175; 2.U.237.240; 2.U.237.244;
 2.U.238.228; 2.U.238.229; 2.U.238.230; 2.U.238.231; 2.U.238.236; 2.U.238.237;
 2.U.238.238; 2.U.238.239; 2.U.238.154; 2.U.238.157; 2.U.238.166; 2.U.238.169;
 2.U.238.172; 2.U.238.175; 2.U.238.240; 2.U.238.244; 2.U.239.228; 2.U.239.229;
 25 2.U.239.230; 2.U.239.231; 2.U.239.236; 2.U.239.237; 2.U.239.238; 2.U.239.239;
 2.U.239.154; 2.U.239.157; 2.U.239.166; 2.U.239.169; 2.U.239.172; 2.U.239.175;
 2.U.239.240; 2.U.239.244; 2.U.154.228; 2.U.154.229; 2.U.154.230; 2.U.154.231;
 2.U.154.236; 2.U.154.237; 2.U.154.238; 2.U.154.239; 2.U.154.154; 2.U.154.157;
 2.U.154.166; 2.U.154.169; 2.U.154.172; 2.U.154.175; 2.U.154.240; 2.U.154.244;
 30 2.U.157.228; 2.U.157.229; 2.U.157.230; 2.U.157.231; 2.U.157.236; 2.U.157.237;
 2.U.157.238; 2.U.157.239; 2.U.157.154; 2.U.157.157; 2.U.157.166; 2.U.157.169;
 2.U.157.172; 2.U.157.175; 2.U.157.240; 2.U.157.244; 2.U.166.228; 2.U.166.229;
 2.U.166.230; 2.U.166.231; 2.U.166.236; 2.U.166.237; 2.U.166.238; 2.U.166.239;
 2.U.166.154; 2.U.166.157; 2.U.166.166; 2.U.166.169; 2.U.166.172; 2.U.166.175;
 35 2.U.166.240; 2.U.166.244; 2.U.169.228; 2.U.169.229; 2.U.169.230; 2.U.169.231;
 2.U.169.236; 2.U.169.237; 2.U.169.238; 2.U.169.239; 2.U.169.154; 2.U.169.157;
 2.U.169.166; 2.U.169.169; 2.U.169.172; 2.U.169.175; 2.U.169.240; 2.U.169.244;
 2.U.172.228; 2.U.172.229; 2.U.172.230; 2.U.172.231; 2.U.172.236; 2.U.172.237;
 2.U.172.238; 2.U.172.239; 2.U.172.154; 2.U.172.157; 2.U.172.166; 2.U.172.169;
 40 2.U.172.172; 2.U.172.175; 2.U.172.240; 2.U.172.244; 2.U.175.228; 2.U.175.229;
 2.U.175.230; 2.U.175.231; 2.U.175.236; 2.U.175.237; 2.U.175.238; 2.U.175.239;
 2.U.175.154; 2.U.175.157; 2.U.175.166; 2.U.175.169; 2.U.175.172; 2.U.175.175;
 2.U.175.240; 2.U.175.244; 2.U.240.228; 2.U.240.229; 2.U.240.230; 2.U.240.231;
 2.U.240.236; 2.U.240.237; 2.U.240.238; 2.U.240.239; 2.U.240.154; 2.U.240.157;
 45 2.U.240.166; 2.U.240.169; 2.U.240.172; 2.U.240.175; 2.U.240.240; 2.U.240.244;
 2.U.244.228; 2.U.244.229; 2.U.244.230; 2.U.244.231; 2.U.244.236; 2.U.244.237;

2.U.244.238; 2.U.244.239; 2.U.244.154; 2.U.244.157; 2.U.244.166; 2.U.244.169;
2.U.244.172; 2.U.244.175; 2.U.244.240; 2.U.244.244;

Prodrugs of 2.W

- 5 2.W.228.228; 2.W.228.229; 2.W.228.230; 2.W.228.231; 2.W.228.236; 2.W.228.237;
2.W.228.238; 2.W.228.239; 2.W.228.154; 2.W.228.157; 2.W.228.166; 2.W.228.169;
2.W.228.172; 2.W.228.175; 2.W.228.240; 2.W.228.244; 2.W.229.228; 2.W.229.229;
2.W.229.230; 2.W.229.231; 2.W.229.236; 2.W.229.237; 2.W.229.238; 2.W.229.239;
2.W.229.154; 2.W.229.157; 2.W.229.166; 2.W.229.169; 2.W.229.172; 2.W.229.175;
10 2.W.229.240; 2.W.229.244; 2.W.230.228; 2.W.230.229; 2.W.230.230; 2.W.230.231;
2.W.230.236; 2.W.230.237; 2.W.230.238; 2.W.230.239; 2.W.230.154; 2.W.230.157;
2.W.230.166; 2.W.230.169; 2.W.230.172; 2.W.230.175; 2.W.230.240; 2.W.230.244;
2.W.231.228; 2.W.231.229; 2.W.231.230; 2.W.231.231; 2.W.231.236; 2.W.231.237;
2.W.231.238; 2.W.231.239; 2.W.231.154; 2.W.231.157; 2.W.231.166; 2.W.231.169;
15 2.W.231.172; 2.W.231.175; 2.W.231.240; 2.W.231.244; 2.W.236.228; 2.W.236.229;
2.W.236.230; 2.W.236.231; 2.W.236.236; 2.W.236.237; 2.W.236.238; 2.W.236.239;
2.W.236.154; 2.W.236.157; 2.W.236.166; 2.W.236.169; 2.W.236.172; 2.W.236.175;
2.W.236.240; 2.W.236.244; 2.W.237.228; 2.W.237.229; 2.W.237.230; 2.W.237.231;
2.W.237.236; 2.W.237.237; 2.W.237.238; 2.W.237.239; 2.W.237.154; 2.W.237.157;
20 2.W.237.166; 2.W.237.169; 2.W.237.172; 2.W.237.175; 2.W.237.240; 2.W.237.244;
2.W.238.228; 2.W.238.229; 2.W.238.230; 2.W.238.231; 2.W.238.236; 2.W.238.237;
2.W.238.238; 2.W.238.239; 2.W.238.154; 2.W.238.157; 2.W.238.166; 2.W.238.169;
2.W.238.172; 2.W.238.175; 2.W.238.240; 2.W.238.244; 2.W.239.228; 2.W.239.229;
2.W.239.230; 2.W.239.231; 2.W.239.236; 2.W.239.237; 2.W.239.238; 2.W.239.239;
25 2.W.239.154; 2.W.239.157; 2.W.239.166; 2.W.239.169; 2.W.239.172; 2.W.239.175;
2.W.239.240; 2.W.239.244; 2.W.154.228; 2.W.154.229; 2.W.154.230; 2.W.154.231;
2.W.154.236; 2.W.154.237; 2.W.154.238; 2.W.154.239; 2.W.154.154; 2.W.154.157;
2.W.154.166; 2.W.154.169; 2.W.154.172; 2.W.154.175; 2.W.154.240; 2.W.154.244;
2.W.157.228; 2.W.157.229; 2.W.157.230; 2.W.157.231; 2.W.157.236; 2.W.157.237;
30 2.W.157.238; 2.W.157.239; 2.W.157.154; 2.W.157.157; 2.W.157.166; 2.W.157.169;
2.W.157.172; 2.W.157.175; 2.W.157.240; 2.W.157.244; 2.W.166.228; 2.W.166.229;
2.W.166.230; 2.W.166.231; 2.W.166.236; 2.W.166.237; 2.W.166.238; 2.W.166.239;
2.W.166.154; 2.W.166.157; 2.W.166.166; 2.W.166.169; 2.W.166.172; 2.W.166.175;
2.W.166.240; 2.W.166.244; 2.W.169.228; 2.W.169.229; 2.W.169.230; 2.W.169.231;
35 2.W.169.236; 2.W.169.237; 2.W.169.238; 2.W.169.239; 2.W.169.154; 2.W.169.157;
2.W.169.166; 2.W.169.169; 2.W.169.172; 2.W.169.175; 2.W.169.240; 2.W.169.244;
2.W.172.228; 2.W.172.229; 2.W.172.230; 2.W.172.231; 2.W.172.236; 2.W.172.237;
2.W.172.238; 2.W.172.239; 2.W.172.154; 2.W.172.157; 2.W.172.166; 2.W.172.169;
2.W.172.172; 2.W.172.175; 2.W.172.240; 2.W.172.244; 2.W.175.228; 2.W.175.229;
40 2.W.175.230; 2.W.175.231; 2.W.175.236; 2.W.175.237; 2.W.175.238; 2.W.175.239;
2.W.175.154; 2.W.175.157; 2.W.175.166; 2.W.175.169; 2.W.175.172; 2.W.175.175;
2.W.175.240; 2.W.175.244; 2.W.240.228; 2.W.240.229; 2.W.240.230; 2.W.240.231;
2.W.240.236; 2.W.240.237; 2.W.240.238; 2.W.240.239; 2.W.240.154; 2.W.240.157;
2.W.240.166; 2.W.240.169; 2.W.240.172; 2.W.240.175; 2.W.240.240; 2.W.240.244;
45 2.W.244.228; 2.W.244.229; 2.W.244.230; 2.W.244.231; 2.W.244.236; 2.W.244.237;

2.W.244.238; 2.W.244.239; 2.W.244.154; 2.W.244.157; 2.W.244.166; 2.W.244.169;
2.W.244.172; 2.W.244.175; 2.W.244.240; 2.W.244.244;

Prodrugs of 2.Y

- 5 2.Y.228.228; 2.Y.228.229; 2.Y.228.230; 2.Y.228.231; 2.Y.228.236; 2.Y.228.237;
2.Y.228.238; 2.Y.228.239; 2.Y.228.154; 2.Y.228.157; 2.Y.228.166; 2.Y.228.169;
2.Y.228.172; 2.Y.228.175; 2.Y.228.240; 2.Y.228.244; 2.Y.229.228; 2.Y.229.229;
2.Y.229.230; 2.Y.229.231; 2.Y.229.236; 2.Y.229.237; 2.Y.229.238; 2.Y.229.239;
2.Y.229.154; 2.Y.229.157; 2.Y.229.166; 2.Y.229.169; 2.Y.229.172; 2.Y.229.175;
10 2.Y.229.240; 2.Y.229.244; 2.Y.230.228; 2.Y.230.229; 2.Y.230.230; 2.Y.230.231;
2.Y.230.236; 2.Y.230.237; 2.Y.230.238; 2.Y.230.239; 2.Y.230.154; 2.Y.230.157;
2.Y.230.166; 2.Y.230.169; 2.Y.230.172; 2.Y.230.175; 2.Y.230.240; 2.Y.230.244;
2.Y.231.228; 2.Y.231.229; 2.Y.231.230; 2.Y.231.231; 2.Y.231.236; 2.Y.231.237;
2.Y.231.238; 2.Y.231.239; 2.Y.231.154; 2.Y.231.157; 2.Y.231.166; 2.Y.231.169;
15 2.Y.231.172; 2.Y.231.175; 2.Y.231.240; 2.Y.231.244; 2.Y.236.228; 2.Y.236.229;
2.Y.236.230; 2.Y.236.231; 2.Y.236.236; 2.Y.236.237; 2.Y.236.238; 2.Y.236.239;
2.Y.236.154; 2.Y.236.157; 2.Y.236.166; 2.Y.236.169; 2.Y.236.172; 2.Y.236.175;
2.Y.236.240; 2.Y.236.244; 2.Y.237.228; 2.Y.237.229; 2.Y.237.230; 2.Y.237.231;
2.Y.237.236; 2.Y.237.237; 2.Y.237.238; 2.Y.237.239; 2.Y.237.154; 2.Y.237.157;
20 2.Y.237.166; 2.Y.237.169; 2.Y.237.172; 2.Y.237.175; 2.Y.237.240; 2.Y.237.244;
2.Y.238.228; 2.Y.238.229; 2.Y.238.230; 2.Y.238.231; 2.Y.238.236; 2.Y.238.237;
2.Y.238.238; 2.Y.238.239; 2.Y.238.154; 2.Y.238.157; 2.Y.238.166; 2.Y.238.169;
2.Y.238.172; 2.Y.238.175; 2.Y.238.240; 2.Y.238.244; 2.Y.239.228; 2.Y.239.229;
2.Y.239.230; 2.Y.239.231; 2.Y.239.236; 2.Y.239.237; 2.Y.239.238; 2.Y.239.239;
25 2.Y.239.154; 2.Y.239.157; 2.Y.239.166; 2.Y.239.169; 2.Y.239.172; 2.Y.239.175;
2.Y.239.240; 2.Y.239.244; 2.Y.154.228; 2.Y.154.229; 2.Y.154.230; 2.Y.154.231;
2.Y.154.236; 2.Y.154.237; 2.Y.154.238; 2.Y.154.239; 2.Y.154.154; 2.Y.154.157;
2.Y.154.166; 2.Y.154.169; 2.Y.154.172; 2.Y.154.175; 2.Y.154.240; 2.Y.154.244;
2.Y.157.228; 2.Y.157.229; 2.Y.157.230; 2.Y.157.231; 2.Y.157.236; 2.Y.157.237;
30 2.Y.157.238; 2.Y.157.239; 2.Y.157.154; 2.Y.157.157; 2.Y.157.166; 2.Y.157.169;
2.Y.157.172; 2.Y.157.175; 2.Y.157.240; 2.Y.157.244; 2.Y.166.228; 2.Y.166.229;
2.Y.166.230; 2.Y.166.231; 2.Y.166.236; 2.Y.166.237; 2.Y.166.238; 2.Y.166.239;
2.Y.166.154; 2.Y.166.157; 2.Y.166.166; 2.Y.166.169; 2.Y.166.172; 2.Y.166.175;
2.Y.166.240; 2.Y.166.244; 2.Y.169.228; 2.Y.169.229; 2.Y.169.230; 2.Y.169.231;
35 2.Y.169.236; 2.Y.169.237; 2.Y.169.238; 2.Y.169.239; 2.Y.169.154; 2.Y.169.157;
2.Y.169.166; 2.Y.169.169; 2.Y.169.172; 2.Y.169.175; 2.Y.169.240; 2.Y.169.244;
2.Y.172.228; 2.Y.172.229; 2.Y.172.230; 2.Y.172.231; 2.Y.172.236; 2.Y.172.237;
2.Y.172.238; 2.Y.172.239; 2.Y.172.154; 2.Y.172.157; 2.Y.172.166; 2.Y.172.169;
2.Y.172.172; 2.Y.172.175; 2.Y.172.240; 2.Y.172.244; 2.Y.175.228; 2.Y.175.229;
40 2.Y.175.230; 2.Y.175.231; 2.Y.175.236; 2.Y.175.237; 2.Y.175.238; 2.Y.175.239;
2.Y.175.154; 2.Y.175.157; 2.Y.175.166; 2.Y.175.169; 2.Y.175.172; 2.Y.175.175;
2.Y.175.240; 2.Y.175.244; 2.Y.240.228; 2.Y.240.229; 2.Y.240.230; 2.Y.240.231;
2.Y.240.236; 2.Y.240.237; 2.Y.240.238; 2.Y.240.239; 2.Y.240.154; 2.Y.240.157;
2.Y.240.166; 2.Y.240.169; 2.Y.240.172; 2.Y.240.175; 2.Y.240.240; 2.Y.240.244;
45 2.Y.244.228; 2.Y.244.229; 2.Y.244.230; 2.Y.244.231; 2.Y.244.236; 2.Y.244.237;

2.Y.244.238; 2.Y.244.239; 2.Y.244.154; 2.Y.244.157; 2.Y.244.166; 2.Y.244.169;
2.Y.244.172; 2.Y.244.175; 2.Y.244.240; 2.Y.244.244;

Prodrugs of 3.B

- 5 3.B.228.228; 3.B.228.229; 3.B.228.230; 3.B.228.231; 3.B.228.236; 3.B.228.237;
3.B.228.238; 3.B.228.239; 3.B.228.154; 3.B.228.157; 3.B.228.166; 3.B.228.169; 3.B.228.172;
3.B.228.175; 3.B.228.240; 3.B.228.244; 3.B.229.228; 3.B.229.229; 3.B.229.230; 3.B.229.231;
3.B.229.236; 3.B.229.237; 3.B.229.238; 3.B.229.239; 3.B.229.154; 3.B.229.157; 3.B.229.166;
3.B.229.169; 3.B.229.172; 3.B.229.175; 3.B.229.240; 3.B.229.244; 3.B.230.228; 3.B.230.229;
10 3.B.230.230; 3.B.230.231; 3.B.230.236; 3.B.230.237; 3.B.230.238; 3.B.230.239; 3.B.230.154;
3.B.230.157; 3.B.230.166; 3.B.230.169; 3.B.230.172; 3.B.230.175; 3.B.230.240; 3.B.230.244;
3.B.231.228; 3.B.231.229; 3.B.231.230; 3.B.231.231; 3.B.231.236; 3.B.231.237; 3.B.231.238;
3.B.231.239; 3.B.231.154; 3.B.231.157; 3.B.231.166; 3.B.231.169; 3.B.231.172; 3.B.231.175;
3.B.231.240; 3.B.231.244; 3.B.236.228; 3.B.236.229; 3.B.236.230; 3.B.236.231; 3.B.236.236;
15 3.B.236.237; 3.B.236.238; 3.B.236.239; 3.B.236.154; 3.B.236.157; 3.B.236.166; 3.B.236.169;
3.B.236.172; 3.B.236.175; 3.B.236.240; 3.B.236.244; 3.B.237.228; 3.B.237.229; 3.B.237.230;
3.B.237.231; 3.B.237.236; 3.B.237.237; 3.B.237.238; 3.B.237.239; 3.B.237.154; 3.B.237.157;
3.B.237.166; 3.B.237.169; 3.B.237.172; 3.B.237.175; 3.B.237.240; 3.B.237.244; 3.B.238.228;
3.B.238.229; 3.B.238.230; 3.B.238.231; 3.B.238.236; 3.B.238.237; 3.B.238.238; 3.B.238.239;
20 3.B.238.154; 3.B.238.157; 3.B.238.166; 3.B.238.169; 3.B.238.172; 3.B.238.175; 3.B.238.240;
3.B.238.244; 3.B.239.228; 3.B.239.229; 3.B.239.230; 3.B.239.231; 3.B.239.236; 3.B.239.237;
3.B.239.238; 3.B.239.239; 3.B.239.154; 3.B.239.157; 3.B.239.166; 3.B.239.169; 3.B.239.172;
3.B.239.175; 3.B.239.240; 3.B.239.244; 3.B.154.228; 3.B.154.229; 3.B.154.230; 3.B.154.231;
3.B.154.236; 3.B.154.237; 3.B.154.238; 3.B.154.239; 3.B.154.154; 3.B.154.157; 3.B.154.166;
25 3.B.154.169; 3.B.154.172; 3.B.154.175; 3.B.154.240; 3.B.154.244; 3.B.157.228; 3.B.157.229;
3.B.157.230; 3.B.157.231; 3.B.157.236; 3.B.157.237; 3.B.157.238; 3.B.157.239; 3.B.157.154;
3.B.157.157; 3.B.157.166; 3.B.157.169; 3.B.157.172; 3.B.157.175; 3.B.157.240; 3.B.157.244;
3.B.166.228; 3.B.166.229; 3.B.166.230; 3.B.166.231; 3.B.166.236; 3.B.166.237; 3.B.166.238;
3.B.166.239; 3.B.166.154; 3.B.166.157; 3.B.166.166; 3.B.166.169; 3.B.166.172; 3.B.166.175;
30 3.B.166.240; 3.B.166.244; 3.B.169.228; 3.B.169.229; 3.B.169.230; 3.B.169.231; 3.B.169.236;
3.B.169.237; 3.B.169.238; 3.B.169.239; 3.B.169.154; 3.B.169.157; 3.B.169.166; 3.B.169.169;
3.B.169.172; 3.B.169.175; 3.B.169.240; 3.B.169.244; 3.B.172.228; 3.B.172.229; 3.B.172.230;
3.B.172.231; 3.B.172.236; 3.B.172.237; 3.B.172.238; 3.B.172.239; 3.B.172.154; 3.B.172.157;
3.B.172.166; 3.B.172.169; 3.B.172.172; 3.B.172.175; 3.B.172.240; 3.B.172.244; 3.B.175.228;
35 3.B.175.229; 3.B.175.230; 3.B.175.231; 3.B.175.236; 3.B.175.237; 3.B.175.238; 3.B.175.239;
3.B.175.154; 3.B.175.157; 3.B.175.166; 3.B.175.169; 3.B.175.172; 3.B.175.175; 3.B.175.240;
3.B.175.244; 3.B.240.228; 3.B.240.229; 3.B.240.230; 3.B.240.231; 3.B.240.236; 3.B.240.237;
3.B.240.238; 3.B.240.239; 3.B.240.154; 3.B.240.157; 3.B.240.166; 3.B.240.169; 3.B.240.172;
3.B.240.175; 3.B.240.240; 3.B.240.244; 3.B.244.228; 3.B.244.229; 3.B.244.230; 3.B.244.231;
40 3.B.244.236; 3.B.244.237; 3.B.244.238; 3.B.244.239; 3.B.244.154; 3.B.244.157; 3.B.244.166;
3.B.244.169; 3.B.244.172; 3.B.244.175; 3.B.244.240; 3.B.244.244;

Prodrugs of 3.D

- 45 3.D.228.228; 3.D.228.229; 3.D.228.230; 3.D.228.231; 3.D.228.236; 3.D.228.237;
3.D.228.238; 3.D.228.239; 3.D.228.154; 3.D.228.157; 3.D.228.166; 3.D.228.169;
3.D.228.172; 3.D.228.175; 3.D.228.240; 3.D.228.244; 3.D.229.228; 3.D.229.229;

3.D.229.230; 3.D.229.231; 3.D.229.236; 3.D.229.237; 3.D.229.238; 3.D.229.239;
 3.D.229.154; 3.D.229.157; 3.D.229.166; 3.D.229.169; 3.D.229.172; 3.D.229.175;
 3.D.229.240; 3.D.229.244; 3.D.230.228; 3.D.230.229; 3.D.230.230; 3.D.230.231;
 3.D.230.236; 3.D.230.237; 3.D.230.238; 3.D.230.239; 3.D.230.154; 3.D.230.157;
 5 3.D.230.166; 3.D.230.169; 3.D.230.172; 3.D.230.175; 3.D.230.240; 3.D.230.244;
 3.D.231.228; 3.D.231.229; 3.D.231.230; 3.D.231.231; 3.D.231.236; 3.D.231.237;
 3.D.231.238; 3.D.231.239; 3.D.231.154; 3.D.231.157; 3.D.231.166; 3.D.231.169;
 3.D.231.172; 3.D.231.175; 3.D.231.240; 3.D.231.244; 3.D.236.228; 3.D.236.229;
 3.D.236.230; 3.D.236.231; 3.D.236.236; 3.D.236.237; 3.D.236.238; 3.D.236.239;
 10 3.D.236.154; 3.D.236.157; 3.D.236.166; 3.D.236.169; 3.D.236.172; 3.D.236.175;
 3.D.236.240; 3.D.236.244; 3.D.237.228; 3.D.237.229; 3.D.237.230; 3.D.237.231;
 3.D.237.236; 3.D.237.237; 3.D.237.238; 3.D.237.239; 3.D.237.154; 3.D.237.157;
 3.D.237.166; 3.D.237.169; 3.D.237.172; 3.D.237.175; 3.D.237.240; 3.D.237.244;
 3.D.238.228; 3.D.238.229; 3.D.238.230; 3.D.238.231; 3.D.238.236; 3.D.238.237;
 15 3.D.238.238; 3.D.238.239; 3.D.238.154; 3.D.238.157; 3.D.238.166; 3.D.238.169;
 3.D.238.172; 3.D.238.175; 3.D.238.240; 3.D.238.244; 3.D.239.228; 3.D.239.229;
 3.D.239.230; 3.D.239.231; 3.D.239.236; 3.D.239.237; 3.D.239.238; 3.D.239.239;
 3.D.239.154; 3.D.239.157; 3.D.239.166; 3.D.239.169; 3.D.239.172; 3.D.239.175;
 3.D.239.240; 3.D.239.244; 3.D.154.228; 3.D.154.229; 3.D.154.230; 3.D.154.231;
 20 3.D.154.236; 3.D.154.237; 3.D.154.238; 3.D.154.239; 3.D.154.154; 3.D.154.157;
 3.D.154.166; 3.D.154.169; 3.D.154.172; 3.D.154.175; 3.D.154.240; 3.D.154.244;
 3.D.157.228; 3.D.157.229; 3.D.157.230; 3.D.157.231; 3.D.157.236; 3.D.157.237;
 3.D.157.238; 3.D.157.239; 3.D.157.154; 3.D.157.157; 3.D.157.166; 3.D.157.169;
 3.D.157.172; 3.D.157.175; 3.D.157.240; 3.D.157.244; 3.D.166.228; 3.D.166.229;
 25 3.D.166.230; 3.D.166.231; 3.D.166.236; 3.D.166.237; 3.D.166.238; 3.D.166.239;
 3.D.166.154; 3.D.166.157; 3.D.166.166; 3.D.166.169; 3.D.166.172; 3.D.166.175;
 3.D.166.240; 3.D.166.244; 3.D.169.228; 3.D.169.229; 3.D.169.230; 3.D.169.231;
 3.D.169.236; 3.D.169.237; 3.D.169.238; 3.D.169.239; 3.D.169.154; 3.D.169.157;
 3.D.169.166; 3.D.169.169; 3.D.169.172; 3.D.169.175; 3.D.169.240; 3.D.169.244;
 30 3.D.172.228; 3.D.172.229; 3.D.172.230; 3.D.172.231; 3.D.172.236; 3.D.172.237;
 3.D.172.238; 3.D.172.239; 3.D.172.154; 3.D.172.157; 3.D.172.166; 3.D.172.169;
 3.D.172.172; 3.D.172.175; 3.D.172.240; 3.D.172.244; 3.D.175.228; 3.D.175.229;
 3.D.175.230; 3.D.175.231; 3.D.175.236; 3.D.175.237; 3.D.175.238; 3.D.175.239;
 3.D.175.154; 3.D.175.157; 3.D.175.166; 3.D.175.169; 3.D.175.172; 3.D.175.175;
 35 3.D.175.240; 3.D.175.244; 3.D.240.228; 3.D.240.229; 3.D.240.230; 3.D.240.231;
 3.D.240.236; 3.D.240.237; 3.D.240.238; 3.D.240.239; 3.D.240.154; 3.D.240.157;
 3.D.240.166; 3.D.240.169; 3.D.240.172; 3.D.240.175; 3.D.240.240; 3.D.240.244;
 3.D.244.228; 3.D.244.229; 3.D.244.230; 3.D.244.231; 3.D.244.236; 3.D.244.237;
 3.D.244.238; 3.D.244.239; 3.D.244.154; 3.D.244.157; 3.D.244.166; 3.D.244.169;
 40 3.D.244.172; 3.D.244.175; 3.D.244.240; 3.D.244.244;

Prodrugs of 3.E

3.E.228.228; 3.E.228.229; 3.E.228.230; 3.E.228.231; 3.E.228.236; 3.E.228.237;
 3.E.228.238; 3.E.228.239; 3.E.228.154; 3.E.228.157; 3.E.228.166; 3.E.228.169; 3.E.228.172;
 45 3.E.228.175; 3.E.228.240; 3.E.228.244; 3.E.229.228; 3.E.229.229; 3.E.229.230; 3.E.229.231;
 3.E.229.236; 3.E.229.237; 3.E.229.238; 3.E.229.239; 3.E.229.154; 3.E.229.157; 3.E.229.166;

3.E.229.169; 3.E.229.172; 3.E.229.175; 3.E.229.240; 3.E.229.244; 3.E.230.228; 3.E.230.229;
 3.E.230.230; 3.E.230.231; 3.E.230.236; 3.E.230.237; 3.E.230.238; 3.E.230.239; 3.E.230.154;
 3.E.230.157; 3.E.230.166; 3.E.230.169; 3.E.230.172; 3.E.230.175; 3.E.230.240; 3.E.230.244;
 3.E.231.228; 3.E.231.229; 3.E.231.230; 3.E.231.231; 3.E.231.236; 3.E.231.237; 3.E.231.238;
 5 3.E.231.239; 3.E.231.154; 3.E.231.157; 3.E.231.166; 3.E.231.169; 3.E.231.172; 3.E.231.175;
 3.E.231.240; 3.E.231.244; 3.E.236.228; 3.E.236.229; 3.E.236.230; 3.E.236.231; 3.E.236.236;
 3.E.236.237; 3.E.236.238; 3.E.236.239; 3.E.236.154; 3.E.236.157; 3.E.236.166; 3.E.236.169;
 3.E.236.172; 3.E.236.175; 3.E.236.240; 3.E.236.244; 3.E.237.228; 3.E.237.229; 3.E.237.230;
 3.E.237.231; 3.E.237.236; 3.E.237.237; 3.E.237.238; 3.E.237.239; 3.E.237.154; 3.E.237.157;
 10 3.E.237.166; 3.E.237.169; 3.E.237.172; 3.E.237.175; 3.E.237.240; 3.E.237.244; 3.E.238.228;
 3.E.238.229; 3.E.238.230; 3.E.238.231; 3.E.238.236; 3.E.238.237; 3.E.238.238; 3.E.238.239;
 3.E.238.154; 3.E.238.157; 3.E.238.166; 3.E.238.169; 3.E.238.172; 3.E.238.175; 3.E.238.240;
 3.E.238.244; 3.E.239.228; 3.E.239.229; 3.E.239.230; 3.E.239.231; 3.E.239.236; 3.E.239.237;
 3.E.239.238; 3.E.239.239; 3.E.239.154; 3.E.239.157; 3.E.239.166; 3.E.239.169; 3.E.239.172;
 15 3.E.239.175; 3.E.239.240; 3.E.239.244; 3.E.154.228; 3.E.154.229; 3.E.154.230; 3.E.154.231;
 3.E.154.236; 3.E.154.237; 3.E.154.238; 3.E.154.239; 3.E.154.154; 3.E.154.157; 3.E.154.166;
 3.E.154.169; 3.E.154.172; 3.E.154.175; 3.E.154.240; 3.E.154.244; 3.E.157.228; 3.E.157.229;
 3.E.157.230; 3.E.157.231; 3.E.157.236; 3.E.157.237; 3.E.157.238; 3.E.157.239; 3.E.157.154;
 3.E.157.157; 3.E.157.166; 3.E.157.169; 3.E.157.172; 3.E.157.175; 3.E.157.240; 3.E.157.244;
 20 3.E.166.228; 3.E.166.229; 3.E.166.230; 3.E.166.231; 3.E.166.236; 3.E.166.237; 3.E.166.238;
 3.E.166.239; 3.E.166.154; 3.E.166.157; 3.E.166.166; 3.E.166.169; 3.E.166.172; 3.E.166.175;
 3.E.166.240; 3.E.166.244; 3.E.169.228; 3.E.169.229; 3.E.169.230; 3.E.169.231; 3.E.169.236;
 3.E.169.237; 3.E.169.238; 3.E.169.239; 3.E.169.154; 3.E.169.157; 3.E.169.166; 3.E.169.169;
 3.E.169.172; 3.E.169.175; 3.E.169.240; 3.E.169.244; 3.E.172.228; 3.E.172.229; 3.E.172.230;
 25 3.E.172.231; 3.E.172.236; 3.E.172.237; 3.E.172.238; 3.E.172.239; 3.E.172.154; 3.E.172.157;
 3.E.172.166; 3.E.172.169; 3.E.172.172; 3.E.172.175; 3.E.172.240; 3.E.172.244; 3.E.175.228;
 3.E.175.229; 3.E.175.230; 3.E.175.231; 3.E.175.236; 3.E.175.237; 3.E.175.238; 3.E.175.239;
 3.E.175.154; 3.E.175.157; 3.E.175.166; 3.E.175.169; 3.E.175.172; 3.E.175.175; 3.E.175.240;
 3.E.175.244; 3.E.240.228; 3.E.240.229; 3.E.240.230; 3.E.240.231; 3.E.240.236; 3.E.240.237;
 30 3.E.240.238; 3.E.240.239; 3.E.240.154; 3.E.240.157; 3.E.240.166; 3.E.240.169; 3.E.240.172;
 3.E.240.175; 3.E.240.240; 3.E.240.244; 3.E.244.228; 3.E.244.229; 3.E.244.230; 3.E.244.231;
 3.E.244.236; 3.E.244.237; 3.E.244.238; 3.E.244.239; 3.E.244.154; 3.E.244.157; 3.E.244.166;
 3.E.244.169; 3.E.244.172; 3.E.244.175; 3.E.244.240; 3.E.244.244;

35 Prodrugs of 3.G

3.G.228.228; 3.G.228.229; 3.G.228.230; 3.G.228.231; 3.G.228.236; 3.G.228.237;
 3.G.228.238; 3.G.228.239; 3.G.228.154; 3.G.228.157; 3.G.228.166; 3.G.228.169;
 3.G.228.172; 3.G.228.175; 3.G.228.240; 3.G.228.244; 3.G.229.228; 3.G.229.229;
 3.G.229.230; 3.G.229.231; 3.G.229.236; 3.G.229.237; 3.G.229.238; 3.G.229.239;
 40 3.G.229.154; 3.G.229.157; 3.G.229.166; 3.G.229.169; 3.G.229.172; 3.G.229.175;
 3.G.229.240; 3.G.229.244; 3.G.230.228; 3.G.230.229; 3.G.230.230; 3.G.230.231;
 3.G.230.236; 3.G.230.237; 3.G.230.238; 3.G.230.239; 3.G.230.154; 3.G.230.157;
 3.G.230.166; 3.G.230.169; 3.G.230.172; 3.G.230.175; 3.G.230.240; 3.G.230.244;
 3.G.231.228; 3.G.231.229; 3.G.231.230; 3.G.231.231; 3.G.231.236; 3.G.231.237;
 45 3.G.231.238; 3.G.231.239; 3.G.231.154; 3.G.231.157; 3.G.231.166; 3.G.231.169;
 3.G.231.172; 3.G.231.175; 3.G.231.240; 3.G.231.244; 3.G.236.228; 3.G.236.229;

- 3.G.236.230; 3.G.236.231; 3.G.236.236; 3.G.236.237; 3.G.236.238; 3.G.236.239;
 3.G.236.154; 3.G.236.157; 3.G.236.166; 3.G.236.169; 3.G.236.172; 3.G.236.175;
 3.G.236.240; 3.G.236.244; 3.G.237.228; 3.G.237.229; 3.G.237.230; 3.G.237.231;
 3.G.237.236; 3.G.237.237; 3.G.237.238; 3.G.237.239; 3.G.237.154; 3.G.237.157;
 5 3.G.237.166; 3.G.237.169; 3.G.237.172; 3.G.237.175; 3.G.237.240; 3.G.237.244;
 3.G.238.228; 3.G.238.229; 3.G.238.230; 3.G.238.231; 3.G.238.236; 3.G.238.237;
 3.G.238.238; 3.G.238.239; 3.G.238.154; 3.G.238.157; 3.G.238.166; 3.G.238.169;
 3.G.238.172; 3.G.238.175; 3.G.238.240; 3.G.238.244; 3.G.239.228; 3.G.239.229;
 3.G.239.230; 3.G.239.231; 3.G.239.236; 3.G.239.237; 3.G.239.238; 3.G.239.239;
 10 3.G.239.154; 3.G.239.157; 3.G.239.166; 3.G.239.169; 3.G.239.172; 3.G.239.175;
 3.G.239.240; 3.G.239.244; 3.G.154.228; 3.G.154.229; 3.G.154.230; 3.G.154.231;
 3.G.154.236; 3.G.154.237; 3.G.154.238; 3.G.154.239; 3.G.154.154; 3.G.154.157;
 3.G.154.166; 3.G.154.169; 3.G.154.172; 3.G.154.175; 3.G.154.240; 3.G.154.244;
 3.G.157.228; 3.G.157.229; 3.G.157.230; 3.G.157.231; 3.G.157.236; 3.G.157.237;
 15 3.G.157.238; 3.G.157.239; 3.G.157.154; 3.G.157.157; 3.G.157.166; 3.G.157.169;
 3.G.157.172; 3.G.157.175; 3.G.157.240; 3.G.157.244; 3.G.166.228; 3.G.166.229;
 3.G.166.230; 3.G.166.231; 3.G.166.236; 3.G.166.237; 3.G.166.238; 3.G.166.239;
 3.G.166.154; 3.G.166.157; 3.G.166.166; 3.G.166.169; 3.G.166.172; 3.G.166.175;
 3.G.166.240; 3.G.166.244; 3.G.169.228; 3.G.169.229; 3.G.169.230; 3.G.169.231;
 20 3.G.169.236; 3.G.169.237; 3.G.169.238; 3.G.169.239; 3.G.169.154; 3.G.169.157;
 3.G.169.166; 3.G.169.169; 3.G.169.172; 3.G.169.175; 3.G.169.240; 3.G.169.244;
 3.G.172.228; 3.G.172.229; 3.G.172.230; 3.G.172.231; 3.G.172.236; 3.G.172.237;
 3.G.172.238; 3.G.172.239; 3.G.172.154; 3.G.172.157; 3.G.172.166; 3.G.172.169;
 3.G.172.172; 3.G.172.175; 3.G.172.240; 3.G.172.244; 3.G.175.228; 3.G.175.229;
 25 3.G.175.230; 3.G.175.231; 3.G.175.236; 3.G.175.237; 3.G.175.238; 3.G.175.239;
 3.G.175.154; 3.G.175.157; 3.G.175.166; 3.G.175.169; 3.G.175.172; 3.G.175.175;
 3.G.175.240; 3.G.175.244; 3.G.240.228; 3.G.240.229; 3.G.240.230; 3.G.240.231;
 3.G.240.236; 3.G.240.237; 3.G.240.238; 3.G.240.239; 3.G.240.154; 3.G.240.157;
 3.G.240.166; 3.G.240.169; 3.G.240.172; 3.G.240.175; 3.G.240.240; 3.G.240.244;
 30 3.G.244.228; 3.G.244.229; 3.G.244.230; 3.G.244.231; 3.G.244.236; 3.G.244.237;
 3.G.244.238; 3.G.244.239; 3.G.244.154; 3.G.244.157; 3.G.244.166; 3.G.244.169;
 3.G.244.172; 3.G.244.175; 3.G.244.240; 3.G.244.244;

Prodrugs of 3.I

- 35 3.I.228.228; 3.I.228.229; 3.I.228.230; 3.I.228.231; 3.I.228.236; 3.I.228.237; 3.I.228.238;
 3.I.228.239; 3.I.228.154; 3.I.228.157; 3.I.228.166; 3.I.228.169; 3.I.228.172; 3.I.228.175;
 3.I.228.240; 3.I.228.244; 3.I.229.228; 3.I.229.229; 3.I.229.230; 3.I.229.231; 3.I.229.236;
 3.I.229.237; 3.I.229.238; 3.I.229.239; 3.I.229.154; 3.I.229.157; 3.I.229.166; 3.I.229.169;
 3.I.229.172; 3.I.229.175; 3.I.229.240; 3.I.229.244; 3.I.230.228; 3.I.230.229; 3.I.230.230;
 40 3.I.230.231; 3.I.230.236; 3.I.230.237; 3.I.230.238; 3.I.230.239; 3.I.230.154; 3.I.230.157;
 3.I.230.166; 3.I.230.169; 3.I.230.172; 3.I.230.175; 3.I.230.240; 3.I.230.244; 3.I.231.228;
 3.I.231.229; 3.I.231.230; 3.I.231.231; 3.I.231.236; 3.I.231.237; 3.I.231.238; 3.I.231.239;
 3.I.231.154; 3.I.231.157; 3.I.231.166; 3.I.231.169; 3.I.231.172; 3.I.231.175; 3.I.231.240;
 3.I.231.244; 3.I.236.228; 3.I.236.229; 3.I.236.230; 3.I.236.231; 3.I.236.236; 3.I.236.237;
 45 3.I.236.238; 3.I.236.239; 3.I.236.154; 3.I.236.157; 3.I.236.166; 3.I.236.169; 3.I.236.172;
 3.I.236.175; 3.I.236.240; 3.I.236.244; 3.I.237.228; 3.I.237.229; 3.I.237.230; 3.I.237.231;

3.I.237.236; 3.I.237.237; 3.I.237.238; 3.I.237.239; 3.I.237.154; 3.I.237.157; 3.I.237.166;
 3.I.237.169; 3.I.237.172; 3.I.237.175; 3.I.237.240; 3.I.237.244; 3.I.238.228; 3.I.238.229;
 3.I.238.230; 3.I.238.231; 3.I.238.236; 3.I.238.237; 3.I.238.238; 3.I.238.239; 3.I.238.154;
 3.I.238.157; 3.I.238.166; 3.I.238.169; 3.I.238.172; 3.I.238.175; 3.I.238.240; 3.I.238.244;
 5 3.I.239.228; 3.I.239.229; 3.I.239.230; 3.I.239.231; 3.I.239.236; 3.I.239.237; 3.I.239.238;
 3.I.239.239; 3.I.239.154; 3.I.239.157; 3.I.239.166; 3.I.239.169; 3.I.239.172; 3.I.239.175;
 3.I.239.240; 3.I.239.244; 3.I.154.228; 3.I.154.229; 3.I.154.230; 3.I.154.231; 3.I.154.236;
 3.I.154.237; 3.I.154.238; 3.I.154.239; 3.I.154.154; 3.I.154.157; 3.I.154.166; 3.I.154.169;
 10 3.I.154.172; 3.I.154.175; 3.I.154.240; 3.I.154.244; 3.I.157.228; 3.I.157.229; 3.I.157.230;
 3.I.157.231; 3.I.157.236; 3.I.157.237; 3.I.157.238; 3.I.157.239; 3.I.157.154; 3.I.157.157;
 3.I.157.166; 3.I.157.169; 3.I.157.172; 3.I.157.175; 3.I.157.240; 3.I.157.244; 3.I.166.228;
 3.I.166.229; 3.I.166.230; 3.I.166.231; 3.I.166.236; 3.I.166.237; 3.I.166.238; 3.I.166.239;
 3.I.166.154; 3.I.166.157; 3.I.166.166; 3.I.166.169; 3.I.166.172; 3.I.166.175; 3.I.166.240;
 3.I.166.244; 3.I.169.228; 3.I.169.229; 3.I.169.230; 3.I.169.231; 3.I.169.236; 3.I.169.237;
 15 3.I.169.238; 3.I.169.239; 3.I.169.154; 3.I.169.157; 3.I.169.166; 3.I.169.169; 3.I.169.172;
 3.I.169.175; 3.I.169.240; 3.I.169.244; 3.I.172.228; 3.I.172.229; 3.I.172.230; 3.I.172.231;
 3.I.172.236; 3.I.172.237; 3.I.172.238; 3.I.172.239; 3.I.172.154; 3.I.172.157; 3.I.172.166;
 3.I.172.169; 3.I.172.172; 3.I.172.175; 3.I.172.240; 3.I.172.244; 3.I.175.228; 3.I.175.229;
 3.I.175.230; 3.I.175.231; 3.I.175.236; 3.I.175.237; 3.I.175.238; 3.I.175.239; 3.I.175.154;
 20 3.I.175.157; 3.I.175.166; 3.I.175.169; 3.I.175.172; 3.I.175.175; 3.I.175.240; 3.I.175.244;
 3.I.240.228; 3.I.240.229; 3.I.240.230; 3.I.240.231; 3.I.240.236; 3.I.240.237; 3.I.240.238;
 3.I.240.239; 3.I.240.154; 3.I.240.157; 3.I.240.166; 3.I.240.169; 3.I.240.172; 3.I.240.175;
 3.I.240.240; 3.I.240.244; 3.I.244.228; 3.I.244.229; 3.I.244.230; 3.I.244.231; 3.I.244.236;
 3.I.244.237; 3.I.244.238; 3.I.244.239; 3.I.244.154; 3.I.244.157; 3.I.244.166; 3.I.244.169;
 25 3.I.244.172; 3.I.244.175; 3.I.244.240; 3.I.244.244;

Prodrugs of 3.I

3.J.228.228; 3.J.228.229; 3.J.228.230; 3.J.228.231; 3.J.228.236; 3.J.228.237; 3.J.228.238;
 3.J.228.239; 3.J.228.154; 3.J.228.157; 3.J.228.166; 3.J.228.169; 3.J.228.172; 3.J.228.175;
 30 3.J.228.240; 3.J.228.244; 3.J.229.228; 3.J.229.229; 3.J.229.230; 3.J.229.231; 3.J.229.236;
 3.J.229.237; 3.J.229.238; 3.J.229.239; 3.J.229.154; 3.J.229.157; 3.J.229.166; 3.J.229.169;
 3.J.229.172; 3.J.229.175; 3.J.229.240; 3.J.229.244; 3.J.230.228; 3.J.230.229; 3.J.230.230;
 3.J.230.231; 3.J.230.236; 3.J.230.237; 3.J.230.238; 3.J.230.239; 3.J.230.154; 3.J.230.157;
 3.J.230.166; 3.J.230.169; 3.J.230.172; 3.J.230.175; 3.J.230.240; 3.J.230.244; 3.J.231.228;
 35 3.J.231.229; 3.J.231.230; 3.J.231.231; 3.J.231.236; 3.J.231.237; 3.J.231.238; 3.J.231.239;
 3.J.231.154; 3.J.231.157; 3.J.231.166; 3.J.231.169; 3.J.231.172; 3.J.231.175; 3.J.231.240;
 3.J.231.244; 3.J.236.228; 3.J.236.229; 3.J.236.230; 3.J.236.231; 3.J.236.236; 3.J.236.237;
 3.J.236.238; 3.J.236.239; 3.J.236.154; 3.J.236.157; 3.J.236.166; 3.J.236.169; 3.J.236.172;
 3.J.236.175; 3.J.236.240; 3.J.236.244; 3.J.237.228; 3.J.237.229; 3.J.237.230; 3.J.237.231;
 40 3.J.237.236; 3.J.237.237; 3.J.237.238; 3.J.237.239; 3.J.237.154; 3.J.237.157; 3.J.237.166;
 3.J.237.169; 3.J.237.172; 3.J.237.175; 3.J.237.240; 3.J.237.244; 3.J.238.228; 3.J.238.229;
 3.J.238.230; 3.J.238.231; 3.J.238.236; 3.J.238.237; 3.J.238.238; 3.J.238.239; 3.J.238.154;
 3.J.238.157; 3.J.238.166; 3.J.238.169; 3.J.238.172; 3.J.238.175; 3.J.238.240; 3.J.238.244;
 3.J.239.228; 3.J.239.229; 3.J.239.230; 3.J.239.231; 3.J.239.236; 3.J.239.237; 3.J.239.238;
 45 3.J.239.239; 3.J.239.154; 3.J.239.157; 3.J.239.166; 3.J.239.169; 3.J.239.172; 3.J.239.175;
 3.J.239.240; 3.J.239.244; 3.J.154.228; 3.J.154.229; 3.J.154.230; 3.J.154.231; 3.J.154.236;

- 3.J.154.237; 3.J.154.238; 3.J.154.239; 3.J.154.154; 3.J.154.157; 3.J.154.166; 3.J.154.169;
 3.J.154.172; 3.J.154.175; 3.J.154.240; 3.J.154.244; 3.J.157.228; 3.J.157.229; 3.J.157.230;
 3.J.157.231; 3.J.157.236; 3.J.157.237; 3.J.157.238; 3.J.157.239; 3.J.157.154; 3.J.157.157;
 3.J.157.166; 3.J.157.169; 3.J.157.172; 3.J.157.175; 3.J.157.240; 3.J.157.244; 3.J.166.228;
 5 3.J.166.229; 3.J.166.230; 3.J.166.231; 3.J.166.236; 3.J.166.237; 3.J.166.238; 3.J.166.239;
 3.J.166.154; 3.J.166.157; 3.J.166.166; 3.J.166.169; 3.J.166.172; 3.J.166.175; 3.J.166.240;
 3.J.166.244; 3.J.169.228; 3.J.169.229; 3.J.169.230; 3.J.169.231; 3.J.169.236; 3.J.169.237;
 3.J.169.238; 3.J.169.239; 3.J.169.154; 3.J.169.157; 3.J.169.166; 3.J.169.169; 3.J.169.172;
 3.J.169.175; 3.J.169.240; 3.J.169.244; 3.J.172.228; 3.J.172.229; 3.J.172.230; 3.J.172.231;
 10 3.J.172.236; 3.J.172.237; 3.J.172.238; 3.J.172.239; 3.J.172.154; 3.J.172.157; 3.J.172.166;
 3.J.172.169; 3.J.172.172; 3.J.172.175; 3.J.172.240; 3.J.172.244; 3.J.175.228; 3.J.175.229;
 3.J.175.230; 3.J.175.231; 3.J.175.236; 3.J.175.237; 3.J.175.238; 3.J.175.239; 3.J.175.154;
 3.J.175.157; 3.J.175.166; 3.J.175.169; 3.J.175.172; 3.J.175.175; 3.J.175.240; 3.J.175.244;
 3.J.240.228; 3.J.240.229; 3.J.240.230; 3.J.240.231; 3.J.240.236; 3.J.240.237; 3.J.240.238;
 15 3.J.240.239; 3.J.240.154; 3.J.240.157; 3.J.240.166; 3.J.240.169; 3.J.240.172; 3.J.240.175;
 3.J.240.240; 3.J.240.244; 3.J.244.228; 3.J.244.229; 3.J.244.230; 3.J.244.231; 3.J.244.236;
 3.J.244.237; 3.J.244.238; 3.J.244.239; 3.J.244.154; 3.J.244.157; 3.J.244.166; 3.J.244.169;
 3.J.244.172; 3.J.244.175; 3.J.244.240; 3.J.244.244;
- 20 Prodrugs of 3.L
 3.L.228.228; 3.L.228.229; 3.L.228.230; 3.L.228.231; 3.L.228.236; 3.L.228.237;
 3.L.228.238; 3.L.228.239; 3.L.228.154; 3.L.228.157; 3.L.228.166; 3.L.228.169; 3.L.228.172;
 3.L.228.175; 3.L.228.240; 3.L.228.244; 3.L.229.228; 3.L.229.229; 3.L.229.230; 3.L.229.231;
 3.L.229.236; 3.L.229.237; 3.L.229.238; 3.L.229.239; 3.L.229.154; 3.L.229.157; 3.L.229.166;
 25 3.L.229.169; 3.L.229.172; 3.L.229.175; 3.L.229.240; 3.L.229.244; 3.L.230.228; 3.L.230.229;
 3.L.230.230; 3.L.230.231; 3.L.230.236; 3.L.230.237; 3.L.230.238; 3.L.230.239; 3.L.230.154;
 3.L.230.157; 3.L.230.166; 3.L.230.169; 3.L.230.172; 3.L.230.175; 3.L.230.240; 3.L.230.244;
 3.L.231.228; 3.L.231.229; 3.L.231.230; 3.L.231.231; 3.L.231.236; 3.L.231.237; 3.L.231.238;
 3.L.231.239; 3.L.231.154; 3.L.231.157; 3.L.231.166; 3.L.231.169; 3.L.231.172; 3.L.231.175;
 30 3.L.231.240; 3.L.231.244; 3.L.236.228; 3.L.236.229; 3.L.236.230; 3.L.236.231; 3.L.236.236;
 3.L.236.237; 3.L.236.238; 3.L.236.239; 3.L.236.154; 3.L.236.157; 3.L.236.166; 3.L.236.169;
 3.L.236.172; 3.L.236.175; 3.L.236.240; 3.L.236.244; 3.L.237.228; 3.L.237.229; 3.L.237.230;
 3.L.237.231; 3.L.237.236; 3.L.237.237; 3.L.237.238; 3.L.237.239; 3.L.237.154; 3.L.237.157;
 3.L.237.166; 3.L.237.169; 3.L.237.172; 3.L.237.175; 3.L.237.240; 3.L.237.244; 3.L.238.228;
 35 3.L.238.229; 3.L.238.230; 3.L.238.231; 3.L.238.236; 3.L.238.237; 3.L.238.238; 3.L.238.239;
 3.L.238.154; 3.L.238.157; 3.L.238.166; 3.L.238.169; 3.L.238.172; 3.L.238.175; 3.L.238.240;
 3.L.238.244; 3.L.239.228; 3.L.239.229; 3.L.239.230; 3.L.239.231; 3.L.239.236; 3.L.239.237;
 3.L.239.238; 3.L.239.239; 3.L.239.154; 3.L.239.157; 3.L.239.166; 3.L.239.169; 3.L.239.172;
 3.L.239.175; 3.L.239.240; 3.L.239.244; 3.L.154.228; 3.L.154.229; 3.L.154.230; 3.L.154.231;
 40 3.L.154.236; 3.L.154.237; 3.L.154.238; 3.L.154.239; 3.L.154.154; 3.L.154.157; 3.L.154.166;
 3.L.154.169; 3.L.154.172; 3.L.154.175; 3.L.154.240; 3.L.154.244; 3.L.157.228; 3.L.157.229;
 3.L.157.230; 3.L.157.231; 3.L.157.236; 3.L.157.237; 3.L.157.238; 3.L.157.239; 3.L.157.154;
 3.L.157.157; 3.L.157.166; 3.L.157.169; 3.L.157.172; 3.L.157.175; 3.L.157.240; 3.L.157.244;
 3.L.166.228; 3.L.166.229; 3.L.166.230; 3.L.166.231; 3.L.166.236; 3.L.166.237; 3.L.166.238;
 45 3.L.166.239; 3.L.166.154; 3.L.166.157; 3.L.166.166; 3.L.166.169; 3.L.166.172; 3.L.166.175;
 3.L.166.240; 3.L.166.244; 3.L.169.228; 3.L.169.229; 3.L.169.230; 3.L.169.231; 3.L.169.236;

3.L.169.237; 3.L.169.238; 3.L.169.239; 3.L.169.154; 3.L.169.157; 3.L.169.166; 3.L.169.169;
 3.L.169.172; 3.L.169.175; 3.L.169.240; 3.L.169.244; 3.L.172.228; 3.L.172.229; 3.L.172.230;
 3.L.172.231; 3.L.172.236; 3.L.172.237; 3.L.172.238; 3.L.172.239; 3.L.172.154; 3.L.172.157;
 3.L.172.166; 3.L.172.169; 3.L.172.172; 3.L.172.175; 3.L.172.240; 3.L.172.244; 3.L.175.228;
 5 3.L.175.229; 3.L.175.230; 3.L.175.231; 3.L.175.236; 3.L.175.237; 3.L.175.238; 3.L.175.239;
 3.L.175.154; 3.L.175.157; 3.L.175.166; 3.L.175.169; 3.L.175.172; 3.L.175.175; 3.L.175.240;
 3.L.175.244; 3.L.240.228; 3.L.240.229; 3.L.240.230; 3.L.240.231; 3.L.240.236; 3.L.240.237;
 3.L.240.238; 3.L.240.239; 3.L.240.154; 3.L.240.157; 3.L.240.166; 3.L.240.169; 3.L.240.172;
 3.L.240.175; 3.L.240.240; 3.L.240.244; 3.L.244.228; 3.L.244.229; 3.L.244.230; 3.L.244.231;
 10 3.L.244.236; 3.L.244.237; 3.L.244.238; 3.L.244.239; 3.L.244.154; 3.L.244.157; 3.L.244.166;
 3.L.244.169; 3.L.244.172; 3.L.244.175; 3.L.244.240; 3.L.244.244;

Prodrugs of 3.O

3.O.228.228; 3.O.228.229; 3.O.228.230; 3.O.228.231; 3.O.228.236; 3.O.228.237;
 15 3.O.228.238; 3.O.228.239; 3.O.228.154; 3.O.228.157; 3.O.228.166; 3.O.228.169;
 3.O.228.172; 3.O.228.175; 3.O.228.240; 3.O.228.244; 3.O.229.228; 3.O.229.229;
 3.O.229.230; 3.O.229.231; 3.O.229.236; 3.O.229.237; 3.O.229.238; 3.O.229.239;
 3.O.229.154; 3.O.229.157; 3.O.229.166; 3.O.229.169; 3.O.229.172; 3.O.229.175;
 20 3.O.229.240; 3.O.229.244; 3.O.230.228; 3.O.230.229; 3.O.230.230; 3.O.230.231;
 3.O.230.236; 3.O.230.237; 3.O.230.238; 3.O.230.239; 3.O.230.154; 3.O.230.157;
 3.O.230.166; 3.O.230.169; 3.O.230.172; 3.O.230.175; 3.O.230.240; 3.O.230.244;
 3.O.231.228; 3.O.231.229; 3.O.231.230; 3.O.231.231; 3.O.231.236; 3.O.231.237;
 3.O.231.238; 3.O.231.239; 3.O.231.154; 3.O.231.157; 3.O.231.166; 3.O.231.169;
 3.O.231.172; 3.O.231.175; 3.O.231.240; 3.O.231.244; 3.O.236.228; 3.O.236.229;
 25 3.O.236.230; 3.O.236.231; 3.O.236.236; 3.O.236.237; 3.O.236.238; 3.O.236.239;
 3.O.236.154; 3.O.236.157; 3.O.236.166; 3.O.236.169; 3.O.236.172; 3.O.236.175;
 3.O.236.240; 3.O.236.244; 3.O.237.228; 3.O.237.229; 3.O.237.230; 3.O.237.231;
 3.O.237.236; 3.O.237.237; 3.O.237.238; 3.O.237.239; 3.O.237.154; 3.O.237.157;
 3.O.237.166; 3.O.237.169; 3.O.237.172; 3.O.237.175; 3.O.237.240; 3.O.237.244;
 30 3.O.238.228; 3.O.238.229; 3.O.238.230; 3.O.238.231; 3.O.238.236; 3.O.238.237;
 3.O.238.238; 3.O.238.239; 3.O.238.154; 3.O.238.157; 3.O.238.166; 3.O.238.169;
 3.O.238.172; 3.O.238.175; 3.O.238.240; 3.O.238.244; 3.O.239.228; 3.O.239.229;
 3.O.239.230; 3.O.239.231; 3.O.239.236; 3.O.239.237; 3.O.239.238; 3.O.239.239;
 3.O.239.154; 3.O.239.157; 3.O.239.166; 3.O.239.169; 3.O.239.172; 3.O.239.175;
 35 3.O.239.240; 3.O.239.244; 3.O.154.228; 3.O.154.229; 3.O.154.230; 3.O.154.231;
 3.O.154.236; 3.O.154.237; 3.O.154.238; 3.O.154.239; 3.O.154.154; 3.O.154.157;
 3.O.154.166; 3.O.154.169; 3.O.154.172; 3.O.154.175; 3.O.154.240; 3.O.154.244;
 3.O.157.228; 3.O.157.229; 3.O.157.230; 3.O.157.231; 3.O.157.236; 3.O.157.237;
 3.O.157.238; 3.O.157.239; 3.O.157.154; 3.O.157.157; 3.O.157.166; 3.O.157.169;
 40 3.O.157.172; 3.O.157.175; 3.O.157.240; 3.O.157.244; 3.O.166.228; 3.O.166.229;
 3.O.166.230; 3.O.166.231; 3.O.166.236; 3.O.166.237; 3.O.166.238; 3.O.166.239;
 3.O.166.154; 3.O.166.157; 3.O.166.166; 3.O.166.169; 3.O.166.172; 3.O.166.175;
 3.O.166.240; 3.O.166.244; 3.O.169.228; 3.O.169.229; 3.O.169.230; 3.O.169.231;
 3.O.169.236; 3.O.169.237; 3.O.169.238; 3.O.169.239; 3.O.169.154; 3.O.169.157;
 45 3.O.169.166; 3.O.169.169; 3.O.169.172; 3.O.169.175; 3.O.169.240; 3.O.169.244;
 3.O.172.228; 3.O.172.229; 3.O.172.230; 3.O.172.231; 3.O.172.236; 3.O.172.237;

3.O.172.238; 3.O.172.239; 3.O.172.154; 3.O.172.157; 3.O.172.166; 3.O.172.169;
 3.O.172.172; 3.O.172.175; 3.O.172.240; 3.O.172.244; 3.O.175.228; 3.O.175.229;
 3.O.175.230; 3.O.175.231; 3.O.175.236; 3.O.175.237; 3.O.175.238; 3.O.175.239;
 3.O.175.154; 3.O.175.157; 3.O.175.166; 3.O.175.169; 3.O.175.172; 3.O.175.175;
 5 3.O.175.240; 3.O.175.244; 3.O.240.228; 3.O.240.229; 3.O.240.230; 3.O.240.231;
 3.O.240.236; 3.O.240.237; 3.O.240.238; 3.O.240.239; 3.O.240.154; 3.O.240.157;
 3.O.240.166; 3.O.240.169; 3.O.240.172; 3.O.240.175; 3.O.240.240; 3.O.240.244;
 3.O.244.228; 3.O.244.229; 3.O.244.230; 3.O.244.231; 3.O.244.236; 3.O.244.237;
 3.O.244.238; 3.O.244.239; 3.O.244.154; 3.O.244.157; 3.O.244.166; 3.O.244.169;
 10 3.O.244.172; 3.O.244.175; 3.O.244.240; 3.O.244.244;

Prodrugs of 3.P

3.P.228.228; 3.P.228.229; 3.P.228.230; 3.P.228.231; 3.P.228.236; 3.P.228.237;
 3.P.228.238; 3.P.228.239; 3.P.228.154; 3.P.228.157; 3.P.228.166; 3.P.228.169; 3.P.228.172;
 15 3.P.228.175; 3.P.228.240; 3.P.228.244; 3.P.229.228; 3.P.229.229; 3.P.229.230; 3.P.229.231;
 3.P.229.236; 3.P.229.237; 3.P.229.238; 3.P.229.239; 3.P.229.154; 3.P.229.157; 3.P.229.166;
 3.P.229.169; 3.P.229.172; 3.P.229.175; 3.P.229.240; 3.P.229.244; 3.P.230.228; 3.P.230.229;
 3.P.230.230; 3.P.230.231; 3.P.230.236; 3.P.230.237; 3.P.230.238; 3.P.230.239; 3.P.230.154;
 3.P.230.157; 3.P.230.166; 3.P.230.169; 3.P.230.172; 3.P.230.175; 3.P.230.240; 3.P.230.244;
 20 3.P.231.228; 3.P.231.229; 3.P.231.230; 3.P.231.231; 3.P.231.236; 3.P.231.237; 3.P.231.238;
 3.P.231.239; 3.P.231.154; 3.P.231.157; 3.P.231.166; 3.P.231.169; 3.P.231.172; 3.P.231.175;
 3.P.231.240; 3.P.231.244; 3.P.236.228; 3.P.236.229; 3.P.236.230; 3.P.236.231; 3.P.236.236;
 3.P.236.237; 3.P.236.238; 3.P.236.239; 3.P.236.154; 3.P.236.157; 3.P.236.166; 3.P.236.169;
 3.P.236.172; 3.P.236.175; 3.P.236.240; 3.P.236.244; 3.P.237.228; 3.P.237.229; 3.P.237.230;
 25 3.P.237.231; 3.P.237.236; 3.P.237.237; 3.P.237.238; 3.P.237.239; 3.P.237.154; 3.P.237.157;
 3.P.237.166; 3.P.237.169; 3.P.237.172; 3.P.237.175; 3.P.237.240; 3.P.237.244; 3.P.238.228;
 3.P.238.229; 3.P.238.230; 3.P.238.231; 3.P.238.236; 3.P.238.237; 3.P.238.238; 3.P.238.239;
 3.P.238.154; 3.P.238.157; 3.P.238.166; 3.P.238.169; 3.P.238.172; 3.P.238.175; 3.P.238.240;
 3.P.238.244; 3.P.239.228; 3.P.239.229; 3.P.239.230; 3.P.239.231; 3.P.239.236; 3.P.239.237;
 30 3.P.239.238; 3.P.239.239; 3.P.239.154; 3.P.239.157; 3.P.239.166; 3.P.239.169; 3.P.239.172;
 3.P.239.175; 3.P.239.240; 3.P.239.244; 3.P.154.228; 3.P.154.229; 3.P.154.230; 3.P.154.231;
 3.P.154.236; 3.P.154.237; 3.P.154.238; 3.P.154.239; 3.P.154.154; 3.P.154.157; 3.P.154.166;
 3.P.154.169; 3.P.154.172; 3.P.154.175; 3.P.154.240; 3.P.154.244; 3.P.157.228; 3.P.157.229;
 3.P.157.230; 3.P.157.231; 3.P.157.236; 3.P.157.237; 3.P.157.238; 3.P.157.239; 3.P.157.154;
 35 3.P.157.157; 3.P.157.166; 3.P.157.169; 3.P.157.172; 3.P.157.175; 3.P.157.240; 3.P.157.244;
 3.P.166.228; 3.P.166.229; 3.P.166.230; 3.P.166.231; 3.P.166.236; 3.P.166.237; 3.P.166.238;
 3.P.166.239; 3.P.166.154; 3.P.166.157; 3.P.166.166; 3.P.166.169; 3.P.166.172; 3.P.166.175;
 3.P.166.240; 3.P.166.244; 3.P.169.228; 3.P.169.229; 3.P.169.230; 3.P.169.231; 3.P.169.236;
 3.P.169.237; 3.P.169.238; 3.P.169.239; 3.P.169.154; 3.P.169.157; 3.P.169.166; 3.P.169.169;
 40 3.P.169.172; 3.P.169.175; 3.P.169.240; 3.P.169.244; 3.P.172.228; 3.P.172.229; 3.P.172.230;
 3.P.172.231; 3.P.172.236; 3.P.172.237; 3.P.172.238; 3.P.172.239; 3.P.172.154; 3.P.172.157;
 3.P.172.166; 3.P.172.169; 3.P.172.172; 3.P.172.175; 3.P.172.240; 3.P.172.244; 3.P.175.228;
 3.P.175.229; 3.P.175.230; 3.P.175.231; 3.P.175.236; 3.P.175.237; 3.P.175.238; 3.P.175.239;
 3.P.175.154; 3.P.175.157; 3.P.175.166; 3.P.175.169; 3.P.175.172; 3.P.175.175; 3.P.175.240;
 45 3.P.175.244; 3.P.240.228; 3.P.240.229; 3.P.240.230; 3.P.240.231; 3.P.240.236; 3.P.240.237;
 3.P.240.238; 3.P.240.239; 3.P.240.154; 3.P.240.157; 3.P.240.166; 3.P.240.169; 3.P.240.172;

3.P.240.175; 3.P.240.240; 3.P.240.244; 3.P.244.228; 3.P.244.229; 3.P.244.230; 3.P.244.231;
 3.P.244.236; 3.P.244.237; 3.P.244.238; 3.P.244.239; 3.P.244.154; 3.P.244.157; 3.P.244.166;
 3.P.244.169; 3.P.244.172; 3.P.244.175; 3.P.244.240; 3.P.244.244;

5 Prodrugs of 3.U

- 3.U.228.228; 3.U.228.229; 3.U.228.230; 3.U.228.231; 3.U.228.236; 3.U.228.237;
 3.U.228.238; 3.U.228.239; 3.U.228.154; 3.U.228.157; 3.U.228.166; 3.U.228.169;
 3.U.228.172; 3.U.228.175; 3.U.228.240; 3.U.228.244; 3.U.229.228; 3.U.229.229;
 3.U.229.230; 3.U.229.231; 3.U.229.236; 3.U.229.237; 3.U.229.238; 3.U.229.239;
 10 3.U.229.154; 3.U.229.157; 3.U.229.166; 3.U.229.169; 3.U.229.172; 3.U.229.175;
 3.U.229.240; 3.U.229.244; 3.U.230.228; 3.U.230.229; 3.U.230.230; 3.U.230.231;
 3.U.230.236; 3.U.230.237; 3.U.230.238; 3.U.230.239; 3.U.230.154; 3.U.230.157;
 3.U.230.166; 3.U.230.169; 3.U.230.172; 3.U.230.175; 3.U.230.240; 3.U.230.244;
 3.U.231.228; 3.U.231.229; 3.U.231.230; 3.U.231.231; 3.U.231.236; 3.U.231.237;
 15 3.U.231.238; 3.U.231.239; 3.U.231.154; 3.U.231.157; 3.U.231.166; 3.U.231.169;
 3.U.231.172; 3.U.231.175; 3.U.231.240; 3.U.231.244; 3.U.236.228; 3.U.236.229;
 3.U.236.230; 3.U.236.231; 3.U.236.236; 3.U.236.237; 3.U.236.238; 3.U.236.239;
 3.U.236.154; 3.U.236.157; 3.U.236.166; 3.U.236.169; 3.U.236.172; 3.U.236.175;
 3.U.236.240; 3.U.236.244; 3.U.237.228; 3.U.237.229; 3.U.237.230; 3.U.237.231;
 20 3.U.237.236; 3.U.237.237; 3.U.237.238; 3.U.237.239; 3.U.237.154; 3.U.237.157;
 3.U.237.166; 3.U.237.169; 3.U.237.172; 3.U.237.175; 3.U.237.240; 3.U.237.244;
 3.U.238.228; 3.U.238.229; 3.U.238.230; 3.U.238.231; 3.U.238.236; 3.U.238.237;
 3.U.238.238; 3.U.238.239; 3.U.238.154; 3.U.238.157; 3.U.238.166; 3.U.238.169;
 3.U.238.172; 3.U.238.175; 3.U.238.240; 3.U.238.244; 3.U.239.228; 3.U.239.229;
 25 3.U.239.230; 3.U.239.231; 3.U.239.236; 3.U.239.237; 3.U.239.238; 3.U.239.239;
 3.U.239.154; 3.U.239.157; 3.U.239.166; 3.U.239.169; 3.U.239.172; 3.U.239.175;
 3.U.239.240; 3.U.239.244; 3.U.154.228; 3.U.154.229; 3.U.154.230; 3.U.154.231;
 3.U.154.236; 3.U.154.237; 3.U.154.238; 3.U.154.239; 3.U.154.154; 3.U.154.157;
 3.U.154.166; 3.U.154.169; 3.U.154.172; 3.U.154.175; 3.U.154.240; 3.U.154.244;
 30 3.U.157.228; 3.U.157.229; 3.U.157.230; 3.U.157.231; 3.U.157.236; 3.U.157.237;
 3.U.157.238; 3.U.157.239; 3.U.157.154; 3.U.157.157; 3.U.157.166; 3.U.157.169;
 3.U.157.172; 3.U.157.175; 3.U.157.240; 3.U.157.244; 3.U.166.228; 3.U.166.229;
 3.U.166.230; 3.U.166.231; 3.U.166.236; 3.U.166.237; 3.U.166.238; 3.U.166.239;
 3.U.166.154; 3.U.166.157; 3.U.166.166; 3.U.166.169; 3.U.166.172; 3.U.166.175;
 35 3.U.166.240; 3.U.166.244; 3.U.169.228; 3.U.169.229; 3.U.169.230; 3.U.169.231;
 3.U.169.236; 3.U.169.237; 3.U.169.238; 3.U.169.239; 3.U.169.154; 3.U.169.157;
 3.U.169.166; 3.U.169.169; 3.U.169.172; 3.U.169.175; 3.U.169.240; 3.U.169.244;
 3.U.172.228; 3.U.172.229; 3.U.172.230; 3.U.172.231; 3.U.172.236; 3.U.172.237;
 3.U.172.238; 3.U.172.239; 3.U.172.154; 3.U.172.157; 3.U.172.166; 3.U.172.169;
 40 3.U.172.172; 3.U.172.175; 3.U.172.240; 3.U.172.244; 3.U.175.228; 3.U.175.229;
 3.U.175.230; 3.U.175.231; 3.U.175.236; 3.U.175.237; 3.U.175.238; 3.U.175.239;
 3.U.175.154; 3.U.175.157; 3.U.175.166; 3.U.175.169; 3.U.175.172; 3.U.175.175;
 3.U.175.240; 3.U.175.244; 3.U.240.228; 3.U.240.229; 3.U.240.230; 3.U.240.231;
 3.U.240.236; 3.U.240.237; 3.U.240.238; 3.U.240.239; 3.U.240.154; 3.U.240.157;
 45 3.U.240.166; 3.U.240.169; 3.U.240.172; 3.U.240.175; 3.U.240.240; 3.U.240.244;
 3.U.244.228; 3.U.244.229; 3.U.244.230; 3.U.244.231; 3.U.244.236; 3.U.244.237;

3.U.244.238; 3.U.244.239; 3.U.244.154; 3.U.244.157; 3.U.244.166; 3.U.244.169;
3.U.244.172; 3.U.244.175; 3.U.244.240; 3.U.244.244;

Prodrugs of 3.W

- 5 3.W.228.228; 3.W.228.229; 3.W.228.230; 3.W.228.231; 3.W.228.236; 3.W.228.237;
3.W.228.238; 3.W.228.239; 3.W.228.154; 3.W.228.157; 3.W.228.166; 3.W.228.169;
3.W.228.172; 3.W.228.175; 3.W.228.240; 3.W.228.244; 3.W.229.228; 3.W.229.229;
3.W.229.230; 3.W.229.231; 3.W.229.236; 3.W.229.237; 3.W.229.238; 3.W.229.239;
3.W.229.154; 3.W.229.157; 3.W.229.166; 3.W.229.169; 3.W.229.172; 3.W.229.175;
10 3.W.229.240; 3.W.229.244; 3.W.230.228; 3.W.230.229; 3.W.230.230; 3.W.230.231;
3.W.230.236; 3.W.230.237; 3.W.230.238; 3.W.230.239; 3.W.230.154; 3.W.230.157;
3.W.230.166; 3.W.230.169; 3.W.230.172; 3.W.230.175; 3.W.230.240; 3.W.230.244;
3.W.231.228; 3.W.231.229; 3.W.231.230; 3.W.231.231; 3.W.231.236; 3.W.231.237;
3.W.231.238; 3.W.231.239; 3.W.231.154; 3.W.231.157; 3.W.231.166; 3.W.231.169;
15 3.W.231.172; 3.W.231.175; 3.W.231.240; 3.W.231.244; 3.W.236.228; 3.W.236.229;
3.W.236.230; 3.W.236.231; 3.W.236.236; 3.W.236.237; 3.W.236.238; 3.W.236.239;
3.W.236.154; 3.W.236.157; 3.W.236.166; 3.W.236.169; 3.W.236.172; 3.W.236.175;
3.W.236.240; 3.W.236.244; 3.W.237.228; 3.W.237.229; 3.W.237.230; 3.W.237.231;
3.W.237.236; 3.W.237.237; 3.W.237.238; 3.W.237.239; 3.W.237.154; 3.W.237.157;
20 3.W.237.166; 3.W.237.169; 3.W.237.172; 3.W.237.175; 3.W.237.240; 3.W.237.244;
3.W.238.228; 3.W.238.229; 3.W.238.230; 3.W.238.231; 3.W.238.236; 3.W.238.237;
3.W.238.238; 3.W.238.239; 3.W.238.154; 3.W.238.157; 3.W.238.166; 3.W.238.169;
3.W.238.172; 3.W.238.175; 3.W.238.240; 3.W.238.244; 3.W.239.228; 3.W.239.229;
3.W.239.230; 3.W.239.231; 3.W.239.236; 3.W.239.237; 3.W.239.238; 3.W.239.239;
25 3.W.239.154; 3.W.239.157; 3.W.239.166; 3.W.239.169; 3.W.239.172; 3.W.239.175;
3.W.239.240; 3.W.239.244; 3.W.154.228; 3.W.154.229; 3.W.154.230; 3.W.154.231;
3.W.154.236; 3.W.154.237; 3.W.154.238; 3.W.154.239; 3.W.154.154; 3.W.154.157;
3.W.154.166; 3.W.154.169; 3.W.154.172; 3.W.154.175; 3.W.154.240; 3.W.154.244;
3.W.157.228; 3.W.157.229; 3.W.157.230; 3.W.157.231; 3.W.157.236; 3.W.157.237;
30 3.W.157.238; 3.W.157.239; 3.W.157.154; 3.W.157.157; 3.W.157.166; 3.W.157.169;
3.W.157.172; 3.W.157.175; 3.W.157.240; 3.W.157.244; 3.W.166.228; 3.W.166.229;
3.W.166.230; 3.W.166.231; 3.W.166.236; 3.W.166.237; 3.W.166.238; 3.W.166.239;
3.W.166.154; 3.W.166.157; 3.W.166.166; 3.W.166.169; 3.W.166.172; 3.W.166.175;
3.W.166.240; 3.W.166.244; 3.W.169.228; 3.W.169.229; 3.W.169.230; 3.W.169.231;
35 3.W.169.236; 3.W.169.237; 3.W.169.238; 3.W.169.239; 3.W.169.154; 3.W.169.157;
3.W.169.166; 3.W.169.169; 3.W.169.172; 3.W.169.175; 3.W.169.240; 3.W.169.244;
3.W.172.228; 3.W.172.229; 3.W.172.230; 3.W.172.231; 3.W.172.236; 3.W.172.237;
3.W.172.238; 3.W.172.239; 3.W.172.154; 3.W.172.157; 3.W.172.166; 3.W.172.169;
3.W.172.172; 3.W.172.175; 3.W.172.240; 3.W.172.244; 3.W.175.228; 3.W.175.229;
40 3.W.175.230; 3.W.175.231; 3.W.175.236; 3.W.175.237; 3.W.175.238; 3.W.175.239;
3.W.175.154; 3.W.175.157; 3.W.175.166; 3.W.175.169; 3.W.175.172; 3.W.175.175;
3.W.175.240; 3.W.175.244; 3.W.240.228; 3.W.240.229; 3.W.240.230; 3.W.240.231;
3.W.240.236; 3.W.240.237; 3.W.240.238; 3.W.240.239; 3.W.240.154; 3.W.240.157;
3.W.240.166; 3.W.240.169; 3.W.240.172; 3.W.240.175; 3.W.240.240; 3.W.240.244;
45 3.W.244.228; 3.W.244.229; 3.W.244.230; 3.W.244.231; 3.W.244.236; 3.W.244.237;

3.W.244.238; 3.W.244.239; 3.W.244.154; 3.W.244.157; 3.W.244.166; 3.W.244.169;
3.W.244.172; 3.W.244.175; 3.W.244.240; 3.W.244.244;

Prodrugs of 3.Y

- 5 3.Y.228.228; 3.Y.228.229; 3.Y.228.230; 3.Y.228.231; 3.Y.228.236; 3.Y.228.237;
3.Y.228.238; 3.Y.228.239; 3.Y.228.154; 3.Y.228.157; 3.Y.228.166; 3.Y.228.169;
3.Y.228.172; 3.Y.228.175; 3.Y.228.240; 3.Y.228.244; 3.Y.229.228; 3.Y.229.229;
3.Y.229.230; 3.Y.229.231; 3.Y.229.236; 3.Y.229.237; 3.Y.229.238; 3.Y.229.239;
3.Y.229.154; 3.Y.229.157; 3.Y.229.166; 3.Y.229.169; 3.Y.229.172; 3.Y.229.175;
10 3.Y.229.240; 3.Y.229.244; 3.Y.230.228; 3.Y.230.229; 3.Y.230.230; 3.Y.230.231;
3.Y.230.236; 3.Y.230.237; 3.Y.230.238; 3.Y.230.239; 3.Y.230.154; 3.Y.230.157;
3.Y.230.166; 3.Y.230.169; 3.Y.230.172; 3.Y.230.175; 3.Y.230.240; 3.Y.230.244;
3.Y.231.228; 3.Y.231.229; 3.Y.231.230; 3.Y.231.231; 3.Y.231.236; 3.Y.231.237;
3.Y.231.238; 3.Y.231.239; 3.Y.231.154; 3.Y.231.157; 3.Y.231.166; 3.Y.231.169;
15 3.Y.231.172; 3.Y.231.175; 3.Y.231.240; 3.Y.231.244; 3.Y.236.228; 3.Y.236.229;
3.Y.236.230; 3.Y.236.231; 3.Y.236.236; 3.Y.236.237; 3.Y.236.238; 3.Y.236.239;
3.Y.236.154; 3.Y.236.157; 3.Y.236.166; 3.Y.236.169; 3.Y.236.172; 3.Y.236.175;
3.Y.236.240; 3.Y.236.244; 3.Y.237.228; 3.Y.237.229; 3.Y.237.230; 3.Y.237.231;
3.Y.237.236; 3.Y.237.237; 3.Y.237.238; 3.Y.237.239; 3.Y.237.154; 3.Y.237.157;
20 3.Y.237.166; 3.Y.237.169; 3.Y.237.172; 3.Y.237.175; 3.Y.237.240; 3.Y.237.244;
3.Y.238.228; 3.Y.238.229; 3.Y.238.230; 3.Y.238.231; 3.Y.238.236; 3.Y.238.237;
3.Y.238.238; 3.Y.238.239; 3.Y.238.154; 3.Y.238.157; 3.Y.238.166; 3.Y.238.169;
3.Y.238.172; 3.Y.238.175; 3.Y.238.240; 3.Y.238.244; 3.Y.239.228; 3.Y.239.229;
3.Y.239.230; 3.Y.239.231; 3.Y.239.236; 3.Y.239.237; 3.Y.239.238; 3.Y.239.239;
25 3.Y.239.154; 3.Y.239.157; 3.Y.239.166; 3.Y.239.169; 3.Y.239.172; 3.Y.239.175;
3.Y.239.240; 3.Y.239.244; 3.Y.154.228; 3.Y.154.229; 3.Y.154.230; 3.Y.154.231;
3.Y.154.236; 3.Y.154.237; 3.Y.154.238; 3.Y.154.239; 3.Y.154.154; 3.Y.154.157;
3.Y.154.166; 3.Y.154.169; 3.Y.154.172; 3.Y.154.175; 3.Y.154.240; 3.Y.154.244;
3.Y.157.228; 3.Y.157.229; 3.Y.157.230; 3.Y.157.231; 3.Y.157.236; 3.Y.157.237;
30 3.Y.157.238; 3.Y.157.239; 3.Y.157.154; 3.Y.157.157; 3.Y.157.166; 3.Y.157.169;
3.Y.157.172; 3.Y.157.175; 3.Y.157.240; 3.Y.157.244; 3.Y.166.228; 3.Y.166.229;
3.Y.166.230; 3.Y.166.231; 3.Y.166.236; 3.Y.166.237; 3.Y.166.238; 3.Y.166.239;
3.Y.166.154; 3.Y.166.157; 3.Y.166.166; 3.Y.166.169; 3.Y.166.172; 3.Y.166.175;
3.Y.166.240; 3.Y.166.244; 3.Y.169.228; 3.Y.169.229; 3.Y.169.230; 3.Y.169.231;
35 3.Y.169.236; 3.Y.169.237; 3.Y.169.238; 3.Y.169.239; 3.Y.169.154; 3.Y.169.157;
3.Y.169.166; 3.Y.169.169; 3.Y.169.172; 3.Y.169.175; 3.Y.169.240; 3.Y.169.244;
3.Y.172.228; 3.Y.172.229; 3.Y.172.230; 3.Y.172.231; 3.Y.172.236; 3.Y.172.237;
3.Y.172.238; 3.Y.172.239; 3.Y.172.154; 3.Y.172.157; 3.Y.172.166; 3.Y.172.169;
3.Y.172.172; 3.Y.172.175; 3.Y.172.240; 3.Y.172.244; 3.Y.175.228; 3.Y.175.229;
40 3.Y.175.230; 3.Y.175.231; 3.Y.175.236; 3.Y.175.237; 3.Y.175.238; 3.Y.175.239;
3.Y.175.154; 3.Y.175.157; 3.Y.175.166; 3.Y.175.169; 3.Y.175.172; 3.Y.175.175;
3.Y.175.240; 3.Y.175.244; 3.Y.240.228; 3.Y.240.229; 3.Y.240.230; 3.Y.240.231;
3.Y.240.236; 3.Y.240.237; 3.Y.240.238; 3.Y.240.239; 3.Y.240.154; 3.Y.240.157;
3.Y.240.166; 3.Y.240.169; 3.Y.240.172; 3.Y.240.175; 3.Y.240.240; 3.Y.240.244;
45 3.Y.244.228; 3.Y.244.229; 3.Y.244.230; 3.Y.244.231; 3.Y.244.236; 3.Y.244.237;

3.Y.244.238; 3.Y.244.239; 3.Y.244.154; 3.Y.244.157; 3.Y.244.166; 3.Y.244.169;
3.Y.244.172; 3.Y.244.175; 3.Y.244.240; 3.Y.244.244;

Prodrugs of 4.B

- 5 4.B.228.228; 4.B.228.229; 4.B.228.230; 4.B.228.231; 4.B.228.236; 4.B.228.237;
4.B.228.238; 4.B.228.239; 4.B.228.154; 4.B.228.157; 4.B.228.166; 4.B.228.169; 4.B.228.172;
4.B.228.175; 4.B.228.240; 4.B.228.244; 4.B.229.228; 4.B.229.229; 4.B.229.230; 4.B.229.231;
4.B.229.236; 4.B.229.237; 4.B.229.238; 4.B.229.239; 4.B.229.154; 4.B.229.157; 4.B.229.166;
4.B.229.169; 4.B.229.172; 4.B.229.175; 4.B.229.240; 4.B.229.244; 4.B.230.228; 4.B.230.229;
10 4.B.230.230; 4.B.230.231; 4.B.230.236; 4.B.230.237; 4.B.230.238; 4.B.230.239; 4.B.230.154;
4.B.230.157; 4.B.230.166; 4.B.230.169; 4.B.230.172; 4.B.230.175; 4.B.230.240; 4.B.230.244;
4.B.231.228; 4.B.231.229; 4.B.231.230; 4.B.231.231; 4.B.231.236; 4.B.231.237; 4.B.231.238;
4.B.231.239; 4.B.231.154; 4.B.231.157; 4.B.231.166; 4.B.231.169; 4.B.231.172; 4.B.231.175;
4.B.231.240; 4.B.231.244; 4.B.236.228; 4.B.236.229; 4.B.236.230; 4.B.236.231; 4.B.236.236;
15 4.B.236.237; 4.B.236.238; 4.B.236.239; 4.B.236.154; 4.B.236.157; 4.B.236.166; 4.B.236.169;
4.B.236.172; 4.B.236.175; 4.B.236.240; 4.B.236.244; 4.B.237.228; 4.B.237.229; 4.B.237.230;
4.B.237.231; 4.B.237.236; 4.B.237.237; 4.B.237.238; 4.B.237.239; 4.B.237.154; 4.B.237.157;
4.B.237.166; 4.B.237.169; 4.B.237.172; 4.B.237.175; 4.B.237.240; 4.B.237.244; 4.B.238.228;
4.B.238.229; 4.B.238.230; 4.B.238.231; 4.B.238.236; 4.B.238.237; 4.B.238.238; 4.B.238.239;
20 4.B.238.154; 4.B.238.157; 4.B.238.166; 4.B.238.169; 4.B.238.172; 4.B.238.175; 4.B.238.240;
4.B.238.244; 4.B.239.228; 4.B.239.229; 4.B.239.230; 4.B.239.231; 4.B.239.236; 4.B.239.237;
4.B.239.238; 4.B.239.239; 4.B.239.154; 4.B.239.157; 4.B.239.166; 4.B.239.169; 4.B.239.172;
4.B.239.175; 4.B.239.240; 4.B.239.244; 4.B.154.228; 4.B.154.229; 4.B.154.230; 4.B.154.231;
4.B.154.236; 4.B.154.237; 4.B.154.238; 4.B.154.239; 4.B.154.154; 4.B.154.157; 4.B.154.166;
25 4.B.154.169; 4.B.154.172; 4.B.154.175; 4.B.154.240; 4.B.154.244; 4.B.157.228; 4.B.157.229;
4.B.157.230; 4.B.157.231; 4.B.157.236; 4.B.157.237; 4.B.157.238; 4.B.157.239; 4.B.157.154;
4.B.157.157; 4.B.157.166; 4.B.157.169; 4.B.157.172; 4.B.157.175; 4.B.157.240; 4.B.157.244;
4.B.166.228; 4.B.166.229; 4.B.166.230; 4.B.166.231; 4.B.166.236; 4.B.166.237; 4.B.166.238;
4.B.166.239; 4.B.166.154; 4.B.166.157; 4.B.166.166; 4.B.166.169; 4.B.166.172; 4.B.166.175;
30 4.B.166.240; 4.B.166.244; 4.B.169.228; 4.B.169.229; 4.B.169.230; 4.B.169.231; 4.B.169.236;
4.B.169.237; 4.B.169.238; 4.B.169.239; 4.B.169.154; 4.B.169.157; 4.B.169.166; 4.B.169.169;
4.B.169.172; 4.B.169.175; 4.B.169.240; 4.B.169.244; 4.B.172.228; 4.B.172.229; 4.B.172.230;
4.B.172.231; 4.B.172.236; 4.B.172.237; 4.B.172.238; 4.B.172.239; 4.B.172.154; 4.B.172.157;
4.B.172.166; 4.B.172.169; 4.B.172.172; 4.B.172.175; 4.B.172.240; 4.B.172.244; 4.B.175.228;
35 4.B.175.229; 4.B.175.230; 4.B.175.231; 4.B.175.236; 4.B.175.237; 4.B.175.238; 4.B.175.239;
4.B.175.154; 4.B.175.157; 4.B.175.166; 4.B.175.169; 4.B.175.172; 4.B.175.175; 4.B.175.240;
4.B.175.244; 4.B.240.228; 4.B.240.229; 4.B.240.230; 4.B.240.231; 4.B.240.236; 4.B.240.237;
4.B.240.238; 4.B.240.239; 4.B.240.154; 4.B.240.157; 4.B.240.166; 4.B.240.169; 4.B.240.172;
4.B.240.175; 4.B.240.240; 4.B.240.244; 4.B.244.228; 4.B.244.229; 4.B.244.230; 4.B.244.231;
40 4.B.244.236; 4.B.244.237; 4.B.244.238; 4.B.244.239; 4.B.244.154; 4.B.244.157; 4.B.244.166;
4.B.244.169; 4.B.244.172; 4.B.244.175; 4.B.244.240; 4.B.244.244;

Prodrugs of 4.D

- 45 4.D.228.228; 4.D.228.229; 4.D.228.230; 4.D.228.231; 4.D.228.236; 4.D.228.237;
4.D.228.238; 4.D.228.239; 4.D.228.154; 4.D.228.157; 4.D.228.166; 4.D.228.169;
4.D.228.172; 4.D.228.175; 4.D.228.240; 4.D.228.244; 4.D.229.228; 4.D.229.229;

- 4.D.229.230; 4.D.229.231; 4.D.229.236; 4.D.229.237; 4.D.229.238; 4.D.229.239;
 4.D.229.154; 4.D.229.157; 4.D.229.166; 4.D.229.169; 4.D.229.172; 4.D.229.175;
 4.D.229.240; 4.D.229.244; 4.D.230.228; 4.D.230.229; 4.D.230.230; 4.D.230.231;
 4.D.230.236; 4.D.230.237; 4.D.230.238; 4.D.230.239; 4.D.230.154; 4.D.230.157;
 5 4.D.230.166; 4.D.230.169; 4.D.230.172; 4.D.230.175; 4.D.230.240; 4.D.230.244;
 4.D.231.228; 4.D.231.229; 4.D.231.230; 4.D.231.231; 4.D.231.236; 4.D.231.237;
 4.D.231.238; 4.D.231.239; 4.D.231.154; 4.D.231.157; 4.D.231.166; 4.D.231.169;
 4.D.231.172; 4.D.231.175; 4.D.231.240; 4.D.231.244; 4.D.236.228; 4.D.236.229;
 4.D.236.230; 4.D.236.231; 4.D.236.236; 4.D.236.237; 4.D.236.238; 4.D.236.239;
 10 4.D.236.154; 4.D.236.157; 4.D.236.166; 4.D.236.169; 4.D.236.172; 4.D.236.175;
 4.D.236.240; 4.D.236.244; 4.D.237.228; 4.D.237.229; 4.D.237.230; 4.D.237.231;
 4.D.237.236; 4.D.237.237; 4.D.237.238; 4.D.237.239; 4.D.237.154; 4.D.237.157;
 4.D.237.166; 4.D.237.169; 4.D.237.172; 4.D.237.175; 4.D.237.240; 4.D.237.244;
 4.D.238.228; 4.D.238.229; 4.D.238.230; 4.D.238.231; 4.D.238.236; 4.D.238.237;
 15 4.D.238.238; 4.D.238.239; 4.D.238.154; 4.D.238.157; 4.D.238.166; 4.D.238.169;
 4.D.238.172; 4.D.238.175; 4.D.238.240; 4.D.238.244; 4.D.239.228; 4.D.239.229;
 4.D.239.230; 4.D.239.231; 4.D.239.236; 4.D.239.237; 4.D.239.238; 4.D.239.239;
 4.D.239.154; 4.D.239.157; 4.D.239.166; 4.D.239.169; 4.D.239.172; 4.D.239.175;
 4.D.239.240; 4.D.239.244; 4.D.154.228; 4.D.154.229; 4.D.154.230; 4.D.154.231;
 20 4.D.154.236; 4.D.154.237; 4.D.154.238; 4.D.154.239; 4.D.154.154; 4.D.154.157;
 4.D.154.166; 4.D.154.169; 4.D.154.172; 4.D.154.175; 4.D.154.240; 4.D.154.244;
 4.D.157.228; 4.D.157.229; 4.D.157.230; 4.D.157.231; 4.D.157.236; 4.D.157.237;
 4.D.157.238; 4.D.157.239; 4.D.157.154; 4.D.157.157; 4.D.157.166; 4.D.157.169;
 4.D.157.172; 4.D.157.175; 4.D.157.240; 4.D.157.244; 4.D.166.228; 4.D.166.229;
 25 4.D.166.230; 4.D.166.231; 4.D.166.236; 4.D.166.237; 4.D.166.238; 4.D.166.239;
 4.D.166.154; 4.D.166.157; 4.D.166.166; 4.D.166.169; 4.D.166.172; 4.D.166.175;
 4.D.166.240; 4.D.166.244; 4.D.169.228; 4.D.169.229; 4.D.169.230; 4.D.169.231;
 4.D.169.236; 4.D.169.237; 4.D.169.238; 4.D.169.239; 4.D.169.154; 4.D.169.157;
 4.D.169.166; 4.D.169.169; 4.D.169.172; 4.D.169.175; 4.D.169.240; 4.D.169.244;
 30 4.D.172.228; 4.D.172.229; 4.D.172.230; 4.D.172.231; 4.D.172.236; 4.D.172.237;
 4.D.172.238; 4.D.172.239; 4.D.172.154; 4.D.172.157; 4.D.172.166; 4.D.172.169;
 4.D.172.172; 4.D.172.175; 4.D.172.240; 4.D.172.244; 4.D.175.228; 4.D.175.229;
 4.D.175.230; 4.D.175.231; 4.D.175.236; 4.D.175.237; 4.D.175.238; 4.D.175.239;
 4.D.175.154; 4.D.175.157; 4.D.175.166; 4.D.175.169; 4.D.175.172; 4.D.175.175;
 35 4.D.175.240; 4.D.175.244; 4.D.240.228; 4.D.240.229; 4.D.240.230; 4.D.240.231;
 4.D.240.236; 4.D.240.237; 4.D.240.238; 4.D.240.239; 4.D.240.154; 4.D.240.157;
 4.D.240.166; 4.D.240.169; 4.D.240.172; 4.D.240.175; 4.D.240.240; 4.D.240.244;
 4.D.244.228; 4.D.244.229; 4.D.244.230; 4.D.244.231; 4.D.244.236; 4.D.244.237;
 4.D.244.238; 4.D.244.239; 4.D.244.154; 4.D.244.157; 4.D.244.166; 4.D.244.169;
 40 4.D.244.172; 4.D.244.175; 4.D.244.240; 4.D.244.244;

Prodrugs of 4.E

- 4.E.228.228; 4.E.228.229; 4.E.228.230; 4.E.228.231; 4.E.228.236; 4.E.228.237;
 4.E.228.238; 4.E.228.239; 4.E.228.154; 4.E.228.157; 4.E.228.166; 4.E.228.169; 4.E.228.172;
 45 4.E.228.175; 4.E.228.240; 4.E.228.244; 4.E.229.228; 4.E.229.229; 4.E.229.230; 4.E.229.231;
 4.E.229.236; 4.E.229.237; 4.E.229.238; 4.E.229.239; 4.E.229.154; 4.E.229.157; 4.E.229.166;

4.E.229.169; 4.E.229.172; 4.E.229.175; 4.E.229.240; 4.E.229.244; 4.E.230.228; 4.E.230.229;
 4.E.230.230; 4.E.230.231; 4.E.230.236; 4.E.230.237; 4.E.230.238; 4.E.230.239; 4.E.230.154;
 4.E.230.157; 4.E.230.166; 4.E.230.169; 4.E.230.172; 4.E.230.175; 4.E.230.240; 4.E.230.244;
 4.E.231.228; 4.E.231.229; 4.E.231.230; 4.E.231.231; 4.E.231.236; 4.E.231.237; 4.E.231.238;
 5 4.E.231.239; 4.E.231.154; 4.E.231.157; 4.E.231.166; 4.E.231.169; 4.E.231.172; 4.E.231.175;
 4.E.231.240; 4.E.231.244; 4.E.236.228; 4.E.236.229; 4.E.236.230; 4.E.236.231; 4.E.236.236;
 4.E.236.237; 4.E.236.238; 4.E.236.239; 4.E.236.154; 4.E.236.157; 4.E.236.166; 4.E.236.169;
 4.E.236.172; 4.E.236.175; 4.E.236.240; 4.E.236.244; 4.E.237.228; 4.E.237.229; 4.E.237.230;
 4.E.237.231; 4.E.237.236; 4.E.237.237; 4.E.237.238; 4.E.237.239; 4.E.237.154; 4.E.237.157;
 10 4.E.237.166; 4.E.237.169; 4.E.237.172; 4.E.237.175; 4.E.237.240; 4.E.237.244; 4.E.238.228;
 4.E.238.229; 4.E.238.230; 4.E.238.231; 4.E.238.236; 4.E.238.237; 4.E.238.238; 4.E.238.239;
 4.E.238.154; 4.E.238.157; 4.E.238.166; 4.E.238.169; 4.E.238.172; 4.E.238.175; 4.E.238.240;
 4.E.238.244; 4.E.239.228; 4.E.239.229; 4.E.239.230; 4.E.239.231; 4.E.239.236; 4.E.239.237;
 4.E.239.238; 4.E.239.239; 4.E.239.154; 4.E.239.157; 4.E.239.166; 4.E.239.169; 4.E.239.172;
 15 4.E.239.175; 4.E.239.240; 4.E.239.244; 4.E.154.228; 4.E.154.229; 4.E.154.230; 4.E.154.231;
 4.E.154.236; 4.E.154.237; 4.E.154.238; 4.E.154.239; 4.E.154.154; 4.E.154.157; 4.E.154.166;
 4.E.154.169; 4.E.154.172; 4.E.154.175; 4.E.154.240; 4.E.154.244; 4.E.157.228; 4.E.157.229;
 4.E.157.230; 4.E.157.231; 4.E.157.236; 4.E.157.237; 4.E.157.238; 4.E.157.239; 4.E.157.154;
 4.E.157.157; 4.E.157.166; 4.E.157.169; 4.E.157.172; 4.E.157.175; 4.E.157.240; 4.E.157.244;
 20 4.E.166.228; 4.E.166.229; 4.E.166.230; 4.E.166.231; 4.E.166.236; 4.E.166.237; 4.E.166.238;
 4.E.166.239; 4.E.166.154; 4.E.166.157; 4.E.166.166; 4.E.166.169; 4.E.166.172; 4.E.166.175;
 4.E.166.240; 4.E.166.244; 4.E.169.228; 4.E.169.229; 4.E.169.230; 4.E.169.231; 4.E.169.236;
 4.E.169.237; 4.E.169.238; 4.E.169.239; 4.E.169.154; 4.E.169.157; 4.E.169.166; 4.E.169.169;
 4.E.169.172; 4.E.169.175; 4.E.169.240; 4.E.169.244; 4.E.172.228; 4.E.172.229; 4.E.172.230;
 25 4.E.172.231; 4.E.172.236; 4.E.172.237; 4.E.172.238; 4.E.172.239; 4.E.172.154; 4.E.172.157;
 4.E.172.166; 4.E.172.169; 4.E.172.172; 4.E.172.175; 4.E.172.240; 4.E.172.244; 4.E.175.228;
 4.E.175.229; 4.E.175.230; 4.E.175.231; 4.E.175.236; 4.E.175.237; 4.E.175.238; 4.E.175.239;
 4.E.175.154; 4.E.175.157; 4.E.175.166; 4.E.175.169; 4.E.175.172; 4.E.175.175; 4.E.175.240;
 4.E.175.244; 4.E.240.228; 4.E.240.229; 4.E.240.230; 4.E.240.231; 4.E.240.236; 4.E.240.237;
 30 4.E.240.238; 4.E.240.239; 4.E.240.154; 4.E.240.157; 4.E.240.166; 4.E.240.169; 4.E.240.172;
 4.E.240.175; 4.E.240.240; 4.E.240.244; 4.E.244.228; 4.E.244.229; 4.E.244.230; 4.E.244.231;
 4.E.244.236; 4.E.244.237; 4.E.244.238; 4.E.244.239; 4.E.244.154; 4.E.244.157; 4.E.244.166;
 4.E.244.169; 4.E.244.172; 4.E.244.175; 4.E.244.240; 4.E.244.244;

35 Prodrugs of 4.G

4.G.228.228; 4.G.228.229; 4.G.228.230; 4.G.228.231; 4.G.228.236; 4.G.228.237;
 4.G.228.238; 4.G.228.239; 4.G.228.154; 4.G.228.157; 4.G.228.166; 4.G.228.169;
 4.G.228.172; 4.G.228.175; 4.G.228.240; 4.G.228.244; 4.G.229.228; 4.G.229.229;
 4.G.229.230; 4.G.229.231; 4.G.229.236; 4.G.229.237; 4.G.229.238; 4.G.229.239;
 40 4.G.229.154; 4.G.229.157; 4.G.229.166; 4.G.229.169; 4.G.229.172; 4.G.229.175;
 4.G.229.240; 4.G.229.244; 4.G.230.228; 4.G.230.229; 4.G.230.230; 4.G.230.231;
 4.G.230.236; 4.G.230.237; 4.G.230.238; 4.G.230.239; 4.G.230.154; 4.G.230.157;
 4.G.230.166; 4.G.230.169; 4.G.230.172; 4.G.230.175; 4.G.230.240; 4.G.230.244;
 4.G.231.228; 4.G.231.229; 4.G.231.230; 4.G.231.231; 4.G.231.236; 4.G.231.237;
 45 4.G.231.238; 4.G.231.239; 4.G.231.154; 4.G.231.157; 4.G.231.166; 4.G.231.169;
 4.G.231.172; 4.G.231.175; 4.G.231.240; 4.G.231.244; 4.G.236.228; 4.G.236.229;

4.G.236.230; 4.G.236.231; 4.G.236.236; 4.G.236.237; 4.G.236.238; 4.G.236.239;
 4.G.236.154; 4.G.236.157; 4.G.236.166; 4.G.236.169; 4.G.236.172; 4.G.236.175;
 4.G.236.240; 4.G.236.244; 4.G.237.228; 4.G.237.229; 4.G.237.230; 4.G.237.231;
 4.G.237.236; 4.G.237.237; 4.G.237.238; 4.G.237.239; 4.G.237.154; 4.G.237.157;
 5 4.G.237.166; 4.G.237.169; 4.G.237.172; 4.G.237.175; 4.G.237.240; 4.G.237.244;
 4.G.238.228; 4.G.238.229; 4.G.238.230; 4.G.238.231; 4.G.238.236; 4.G.238.237;
 4.G.238.238; 4.G.238.239; 4.G.238.154; 4.G.238.157; 4.G.238.166; 4.G.238.169;
 4.G.238.172; 4.G.238.175; 4.G.238.240; 4.G.238.244; 4.G.239.228; 4.G.239.229;
 10 4.G.239.230; 4.G.239.231; 4.G.239.236; 4.G.239.237; 4.G.239.238; 4.G.239.239;
 4.G.239.154; 4.G.239.157; 4.G.239.166; 4.G.239.169; 4.G.239.172; 4.G.239.175;
 4.G.239.240; 4.G.239.244; 4.G.154.228; 4.G.154.229; 4.G.154.230; 4.G.154.231;
 4.G.154.236; 4.G.154.237; 4.G.154.238; 4.G.154.239; 4.G.154.154; 4.G.154.157;
 4.G.154.166; 4.G.154.169; 4.G.154.172; 4.G.154.175; 4.G.154.240; 4.G.154.244;
 4.G.157.228; 4.G.157.229; 4.G.157.230; 4.G.157.231; 4.G.157.236; 4.G.157.237;
 15 4.G.157.238; 4.G.157.239; 4.G.157.154; 4.G.157.157; 4.G.157.166; 4.G.157.169;
 4.G.157.172; 4.G.157.175; 4.G.157.240; 4.G.157.244; 4.G.166.228; 4.G.166.229;
 4.G.166.230; 4.G.166.231; 4.G.166.236; 4.G.166.237; 4.G.166.238; 4.G.166.239;
 4.G.166.154; 4.G.166.157; 4.G.166.166; 4.G.166.169; 4.G.166.172; 4.G.166.175;
 4.G.166.240; 4.G.166.244; 4.G.169.228; 4.G.169.229; 4.G.169.230; 4.G.169.231;
 20 4.G.169.236; 4.G.169.237; 4.G.169.238; 4.G.169.239; 4.G.169.154; 4.G.169.157;
 4.G.169.166; 4.G.169.169; 4.G.169.172; 4.G.169.175; 4.G.169.240; 4.G.169.244;
 4.G.172.228; 4.G.172.229; 4.G.172.230; 4.G.172.231; 4.G.172.236; 4.G.172.237;
 4.G.172.238; 4.G.172.239; 4.G.172.154; 4.G.172.157; 4.G.172.166; 4.G.172.169;
 4.G.172.172; 4.G.172.175; 4.G.172.240; 4.G.172.244; 4.G.175.228; 4.G.175.229;
 25 4.G.175.230; 4.G.175.231; 4.G.175.236; 4.G.175.237; 4.G.175.238; 4.G.175.239;
 4.G.175.154; 4.G.175.157; 4.G.175.166; 4.G.175.169; 4.G.175.172; 4.G.175.175;
 4.G.175.240; 4.G.175.244; 4.G.240.228; 4.G.240.229; 4.G.240.230; 4.G.240.231;
 4.G.240.236; 4.G.240.237; 4.G.240.238; 4.G.240.239; 4.G.240.154; 4.G.240.157;
 4.G.240.166; 4.G.240.169; 4.G.240.172; 4.G.240.175; 4.G.240.240; 4.G.240.244;
 30 4.G.244.228; 4.G.244.229; 4.G.244.230; 4.G.244.231; 4.G.244.236; 4.G.244.237;
 4.G.244.238; 4.G.244.239; 4.G.244.154; 4.G.244.157; 4.G.244.166; 4.G.244.169;
 4.G.244.172; 4.G.244.175; 4.G.244.240; 4.G.244.244;

Prodrugs of 4.I

35 4.I.228.228; 4.I.228.229; 4.I.228.230; 4.I.228.231; 4.I.228.236; 4.I.228.237; 4.I.228.238;
 4.I.228.239; 4.I.228.154; 4.I.228.157; 4.I.228.166; 4.I.228.169; 4.I.228.172; 4.I.228.175;
 4.I.228.240; 4.I.228.244; 4.I.229.228; 4.I.229.229; 4.I.229.230; 4.I.229.231; 4.I.229.236;
 4.I.229.237; 4.I.229.238; 4.I.229.239; 4.I.229.154; 4.I.229.157; 4.I.229.166; 4.I.229.169;
 4.I.229.172; 4.I.229.175; 4.I.229.240; 4.I.229.244; 4.I.230.228; 4.I.230.229; 4.I.230.230;
 40 4.I.230.231; 4.I.230.236; 4.I.230.237; 4.I.230.238; 4.I.230.239; 4.I.230.154; 4.I.230.157;
 4.I.230.166; 4.I.230.169; 4.I.230.172; 4.I.230.175; 4.I.230.240; 4.I.230.244; 4.I.231.228;
 4.I.231.229; 4.I.231.230; 4.I.231.231; 4.I.231.236; 4.I.231.237; 4.I.231.238; 4.I.231.239;
 4.I.231.154; 4.I.231.157; 4.I.231.166; 4.I.231.169; 4.I.231.172; 4.I.231.175; 4.I.231.240;
 4.I.231.244; 4.I.236.228; 4.I.236.229; 4.I.236.230; 4.I.236.231; 4.I.236.236; 4.I.236.237;
 45 4.I.236.238; 4.I.236.239; 4.I.236.154; 4.I.236.157; 4.I.236.166; 4.I.236.169; 4.I.236.172;
 4.I.236.175; 4.I.236.240; 4.I.236.244; 4.I.237.228; 4.I.237.229; 4.I.237.230; 4.I.237.231;

4.I.237.236; 4.I.237.237; 4.I.237.238; 4.I.237.239; 4.I.237.154; 4.I.237.157; 4.I.237.166;
 4.I.237.169; 4.I.237.172; 4.I.237.175; 4.I.237.240; 4.I.237.244; 4.I.238.228; 4.I.238.229;
 4.I.238.230; 4.I.238.231; 4.I.238.236; 4.I.238.237; 4.I.238.238; 4.I.238.239; 4.I.238.154;
 4.I.238.157; 4.I.238.166; 4.I.238.169; 4.I.238.172; 4.I.238.175; 4.I.238.240; 4.I.238.244;
 5 4.I.239.228; 4.I.239.229; 4.I.239.230; 4.I.239.231; 4.I.239.236; 4.I.239.237; 4.I.239.238;
 4.I.239.239; 4.I.239.154; 4.I.239.157; 4.I.239.166; 4.I.239.169; 4.I.239.172; 4.I.239.175;
 4.I.239.240; 4.I.239.244; 4.I.154.228; 4.I.154.229; 4.I.154.230; 4.I.154.231; 4.I.154.236;
 4.I.154.237; 4.I.154.238; 4.I.154.239; 4.I.154.154; 4.I.154.157; 4.I.154.166; 4.I.154.169;
 4.I.154.172; 4.I.154.175; 4.I.154.240; 4.I.154.244; 4.I.157.228; 4.I.157.229; 4.I.157.230;
 10 4.I.157.231; 4.I.157.236; 4.I.157.237; 4.I.157.238; 4.I.157.239; 4.I.157.154; 4.I.157.157;
 4.I.157.166; 4.I.157.169; 4.I.157.172; 4.I.157.175; 4.I.157.240; 4.I.157.244; 4.I.166.228;
 4.I.166.229; 4.I.166.230; 4.I.166.231; 4.I.166.236; 4.I.166.237; 4.I.166.238; 4.I.166.239;
 4.I.166.154; 4.I.166.157; 4.I.166.166; 4.I.166.169; 4.I.166.172; 4.I.166.175; 4.I.166.240;
 4.I.166.244; 4.I.169.228; 4.I.169.229; 4.I.169.230; 4.I.169.231; 4.I.169.236; 4.I.169.237;
 15 4.I.169.238; 4.I.169.239; 4.I.169.154; 4.I.169.157; 4.I.169.166; 4.I.169.169; 4.I.169.172;
 4.I.169.175; 4.I.169.240; 4.I.169.244; 4.I.172.228; 4.I.172.229; 4.I.172.230; 4.I.172.231;
 4.I.172.236; 4.I.172.237; 4.I.172.238; 4.I.172.239; 4.I.172.154; 4.I.172.157; 4.I.172.166;
 4.I.172.169; 4.I.172.172; 4.I.172.175; 4.I.172.240; 4.I.172.244; 4.I.175.228; 4.I.175.229;
 4.I.175.230; 4.I.175.231; 4.I.175.236; 4.I.175.237; 4.I.175.238; 4.I.175.239; 4.I.175.154;
 20 4.I.175.157; 4.I.175.166; 4.I.175.169; 4.I.175.172; 4.I.175.175; 4.I.175.240; 4.I.175.244;
 4.I.240.228; 4.I.240.229; 4.I.240.230; 4.I.240.231; 4.I.240.236; 4.I.240.237; 4.I.240.238;
 4.I.240.239; 4.I.240.154; 4.I.240.157; 4.I.240.166; 4.I.240.169; 4.I.240.172; 4.I.240.175;
 4.I.240.240; 4.I.240.244; 4.I.244.228; 4.I.244.229; 4.I.244.230; 4.I.244.231; 4.I.244.236;
 4.I.244.237; 4.I.244.238; 4.I.244.239; 4.I.244.154; 4.I.244.157; 4.I.244.166; 4.I.244.169;
 25 4.I.244.172; 4.I.244.175; 4.I.244.240; 4.I.244.244;

Prodrugs of 4.I

4.J.228.228; 4.J.228.229; 4.J.228.230; 4.J.228.231; 4.J.228.236; 4.J.228.237; 4.J.228.238;
 4.J.228.239; 4.J.228.154; 4.J.228.157; 4.J.228.166; 4.J.228.169; 4.J.228.172; 4.J.228.175;
 30 4.J.228.240; 4.J.228.244; 4.J.229.228; 4.J.229.229; 4.J.229.230; 4.J.229.231; 4.J.229.236;
 4.J.229.237; 4.J.229.238; 4.J.229.239; 4.J.229.154; 4.J.229.157; 4.J.229.166; 4.J.229.169;
 4.J.229.172; 4.J.229.175; 4.J.229.240; 4.J.229.244; 4.J.230.228; 4.J.230.229; 4.J.230.230;
 4.J.230.231; 4.J.230.236; 4.J.230.237; 4.J.230.238; 4.J.230.239; 4.J.230.154; 4.J.230.157;
 4.J.230.166; 4.J.230.169; 4.J.230.172; 4.J.230.175; 4.J.230.240; 4.J.230.244; 4.J.231.228;
 35 4.J.231.229; 4.J.231.230; 4.J.231.231; 4.J.231.236; 4.J.231.237; 4.J.231.238; 4.J.231.239;
 4.J.231.154; 4.J.231.157; 4.J.231.166; 4.J.231.169; 4.J.231.172; 4.J.231.175; 4.J.231.240;
 4.J.231.244; 4.J.236.228; 4.J.236.229; 4.J.236.230; 4.J.236.231; 4.J.236.236; 4.J.236.237;
 4.J.236.238; 4.J.236.239; 4.J.236.154; 4.J.236.157; 4.J.236.166; 4.J.236.169; 4.J.236.172;
 4.J.236.175; 4.J.236.240; 4.J.236.244; 4.J.237.228; 4.J.237.229; 4.J.237.230; 4.J.237.231;
 40 4.J.237.236; 4.J.237.237; 4.J.237.238; 4.J.237.239; 4.J.237.154; 4.J.237.157; 4.J.237.166;
 4.J.237.169; 4.J.237.172; 4.J.237.175; 4.J.237.240; 4.J.237.244; 4.J.238.228; 4.J.238.229;
 4.J.238.230; 4.J.238.231; 4.J.238.236; 4.J.238.237; 4.J.238.238; 4.J.238.239; 4.J.238.154;
 4.J.238.157; 4.J.238.166; 4.J.238.169; 4.J.238.172; 4.J.238.175; 4.J.238.240; 4.J.238.244;
 4.J.239.228; 4.J.239.229; 4.J.239.230; 4.J.239.231; 4.J.239.236; 4.J.239.237; 4.J.239.238;
 45 4.J.239.239; 4.J.239.154; 4.J.239.157; 4.J.239.166; 4.J.239.169; 4.J.239.172; 4.J.239.175;
 4.J.239.240; 4.J.239.244; 4.J.154.228; 4.J.154.229; 4.J.154.230; 4.J.154.231; 4.J.154.236;

- 4.J.154.237; 4.J.154.238; 4.J.154.239; 4.J.154.154; 4.J.154.157; 4.J.154.166; 4.J.154.169;
 4.J.154.172; 4.J.154.175; 4.J.154.240; 4.J.154.244; 4.J.157.228; 4.J.157.229; 4.J.157.230;
 4.J.157.231; 4.J.157.236; 4.J.157.237; 4.J.157.238; 4.J.157.239; 4.J.157.154; 4.J.157.157;
 4.J.157.166; 4.J.157.169; 4.J.157.172; 4.J.157.175; 4.J.157.240; 4.J.157.244; 4.J.166.228;
 5 4.J.166.229; 4.J.166.230; 4.J.166.231; 4.J.166.236; 4.J.166.237; 4.J.166.238; 4.J.166.239;
 4.J.166.154; 4.J.166.157; 4.J.166.166; 4.J.166.169; 4.J.166.172; 4.J.166.175; 4.J.166.240;
 4.J.166.244; 4.J.169.228; 4.J.169.229; 4.J.169.230; 4.J.169.231; 4.J.169.236; 4.J.169.237;
 4.J.169.238; 4.J.169.239; 4.J.169.154; 4.J.169.157; 4.J.169.166; 4.J.169.169; 4.J.169.172;
 4.J.169.175; 4.J.169.240; 4.J.169.244; 4.J.172.228; 4.J.172.229; 4.J.172.230; 4.J.172.231;
 10 4.J.172.236; 4.J.172.237; 4.J.172.238; 4.J.172.239; 4.J.172.154; 4.J.172.157; 4.J.172.166;
 4.J.172.169; 4.J.172.172; 4.J.172.175; 4.J.172.240; 4.J.172.244; 4.J.175.228; 4.J.175.229;
 4.J.175.230; 4.J.175.231; 4.J.175.236; 4.J.175.237; 4.J.175.238; 4.J.175.239; 4.J.175.154;
 4.J.175.157; 4.J.175.166; 4.J.175.169; 4.J.175.172; 4.J.175.175; 4.J.175.240; 4.J.175.244;
 4.J.240.228; 4.J.240.229; 4.J.240.230; 4.J.240.231; 4.J.240.236; 4.J.240.237; 4.J.240.238;
 15 4.J.240.239; 4.J.240.154; 4.J.240.157; 4.J.240.166; 4.J.240.169; 4.J.240.172; 4.J.240.175;
 4.J.240.240; 4.J.240.244; 4.J.244.228; 4.J.244.229; 4.J.244.230; 4.J.244.231; 4.J.244.236;
 4.J.244.237; 4.J.244.238; 4.J.244.239; 4.J.244.154; 4.J.244.157; 4.J.244.166; 4.J.244.169;
 4.J.244.172; 4.J.244.175; 4.J.244.240; 4.J.244.244;
- 20 Prodrugs of 4.L
 4.L.228.228; 4.L.228.229; 4.L.228.230; 4.L.228.231; 4.L.228.236; 4.L.228.237;
 4.L.228.238; 4.L.228.239; 4.L.228.154; 4.L.228.157; 4.L.228.166; 4.L.228.169; 4.L.228.172;
 4.L.228.175; 4.L.228.240; 4.L.228.244; 4.L.229.228; 4.L.229.229; 4.L.229.230; 4.L.229.231;
 4.L.229.236; 4.L.229.237; 4.L.229.238; 4.L.229.239; 4.L.229.154; 4.L.229.157; 4.L.229.166;
 25 4.L.229.169; 4.L.229.172; 4.L.229.175; 4.L.229.240; 4.L.229.244; 4.L.230.228; 4.L.230.229;
 4.L.230.230; 4.L.230.231; 4.L.230.236; 4.L.230.237; 4.L.230.238; 4.L.230.239; 4.L.230.154;
 4.L.230.157; 4.L.230.166; 4.L.230.169; 4.L.230.172; 4.L.230.175; 4.L.230.240; 4.L.230.244;
 4.L.231.228; 4.L.231.229; 4.L.231.230; 4.L.231.231; 4.L.231.236; 4.L.231.237; 4.L.231.238;
 4.L.231.239; 4.L.231.154; 4.L.231.157; 4.L.231.166; 4.L.231.169; 4.L.231.172; 4.L.231.175;
 30 4.L.231.240; 4.L.231.244; 4.L.236.228; 4.L.236.229; 4.L.236.230; 4.L.236.231; 4.L.236.236;
 4.L.236.237; 4.L.236.238; 4.L.236.239; 4.L.236.154; 4.L.236.157; 4.L.236.166; 4.L.236.169;
 4.L.236.172; 4.L.236.175; 4.L.236.240; 4.L.236.244; 4.L.237.228; 4.L.237.229; 4.L.237.230;
 4.L.237.231; 4.L.237.236; 4.L.237.237; 4.L.237.238; 4.L.237.239; 4.L.237.154; 4.L.237.157;
 4.L.237.166; 4.L.237.169; 4.L.237.172; 4.L.237.175; 4.L.237.240; 4.L.237.244; 4.L.238.228;
 35 4.L.238.229; 4.L.238.230; 4.L.238.231; 4.L.238.236; 4.L.238.237; 4.L.238.238; 4.L.238.239;
 4.L.238.154; 4.L.238.157; 4.L.238.166; 4.L.238.169; 4.L.238.172; 4.L.238.175; 4.L.238.240;
 4.L.238.244; 4.L.239.228; 4.L.239.229; 4.L.239.230; 4.L.239.231; 4.L.239.236; 4.L.239.237;
 4.L.239.238; 4.L.239.239; 4.L.239.154; 4.L.239.157; 4.L.239.166; 4.L.239.169; 4.L.239.172;
 4.L.239.175; 4.L.239.240; 4.L.239.244; 4.L.154.228; 4.L.154.229; 4.L.154.230; 4.L.154.231;
 40 4.L.154.236; 4.L.154.237; 4.L.154.238; 4.L.154.239; 4.L.154.154; 4.L.154.157; 4.L.154.166;
 4.L.154.169; 4.L.154.172; 4.L.154.175; 4.L.154.240; 4.L.154.244; 4.L.157.228; 4.L.157.229;
 4.L.157.230; 4.L.157.231; 4.L.157.236; 4.L.157.237; 4.L.157.238; 4.L.157.239; 4.L.157.154;
 4.L.157.157; 4.L.157.166; 4.L.157.169; 4.L.157.172; 4.L.157.175; 4.L.157.240; 4.L.157.244;
 4.L.166.228; 4.L.166.229; 4.L.166.230; 4.L.166.231; 4.L.166.236; 4.L.166.237; 4.L.166.238;
 45 4.L.166.239; 4.L.166.154; 4.L.166.157; 4.L.166.166; 4.L.166.169; 4.L.166.172; 4.L.166.175;
 4.L.166.240; 4.L.166.244; 4.L.169.228; 4.L.169.229; 4.L.169.230; 4.L.169.231; 4.L.169.236;

4.L.169.237; 4.L.169.238; 4.L.169.239; 4.L.169.154; 4.L.169.157; 4.L.169.166; 4.L.169.169;
 4.L.169.172; 4.L.169.175; 4.L.169.240; 4.L.169.244; 4.L.172.228; 4.L.172.229; 4.L.172.230;
 4.L.172.231; 4.L.172.236; 4.L.172.237; 4.L.172.238; 4.L.172.239; 4.L.172.154; 4.L.172.157;
 4.L.172.166; 4.L.172.169; 4.L.172.172; 4.L.172.175; 4.L.172.240; 4.L.172.244; 4.L.175.228;
 5 4.L.175.229; 4.L.175.230; 4.L.175.231; 4.L.175.236; 4.L.175.237; 4.L.175.238; 4.L.175.239;
 4.L.175.154; 4.L.175.157; 4.L.175.166; 4.L.175.169; 4.L.175.172; 4.L.175.175; 4.L.175.240;
 4.L.175.244; 4.L.240.228; 4.L.240.229; 4.L.240.230; 4.L.240.231; 4.L.240.236; 4.L.240.237;
 4.L.240.238; 4.L.240.239; 4.L.240.154; 4.L.240.157; 4.L.240.166; 4.L.240.169; 4.L.240.172;
 4.L.240.175; 4.L.240.240; 4.L.240.244; 4.L.244.228; 4.L.244.229; 4.L.244.230; 4.L.244.231;
 10 4.L.244.236; 4.L.244.237; 4.L.244.238; 4.L.244.239; 4.L.244.154; 4.L.244.157; 4.L.244.166;
 4.L.244.169; 4.L.244.172; 4.L.244.175; 4.L.244.240; 4.L.244.244;

Prodrugs of 4.O

4.O.228.228; 4.O.228.229; 4.O.228.230; 4.O.228.231; 4.O.228.236; 4.O.228.237;
 15 4.O.228.238; 4.O.228.239; 4.O.228.154; 4.O.228.157; 4.O.228.166; 4.O.228.169;
 4.O.228.172; 4.O.228.175; 4.O.228.240; 4.O.228.244; 4.O.229.228; 4.O.229.229;
 4.O.229.230; 4.O.229.231; 4.O.229.236; 4.O.229.237; 4.O.229.238; 4.O.229.239;
 4.O.229.154; 4.O.229.157; 4.O.229.166; 4.O.229.169; 4.O.229.172; 4.O.229.175;
 4.O.229.240; 4.O.229.244; 4.O.230.228; 4.O.230.229; 4.O.230.230; 4.O.230.231;
 20 4.O.230.236; 4.O.230.237; 4.O.230.238; 4.O.230.239; 4.O.230.154; 4.O.230.157;
 4.O.230.166; 4.O.230.169; 4.O.230.172; 4.O.230.175; 4.O.230.240; 4.O.230.244;
 4.O.231.228; 4.O.231.229; 4.O.231.230; 4.O.231.231; 4.O.231.236; 4.O.231.237;
 4.O.231.238; 4.O.231.239; 4.O.231.154; 4.O.231.157; 4.O.231.166; 4.O.231.169;
 4.O.231.172; 4.O.231.175; 4.O.231.240; 4.O.231.244; 4.O.236.228; 4.O.236.229;
 25 4.O.236.230; 4.O.236.231; 4.O.236.236; 4.O.236.237; 4.O.236.238; 4.O.236.239;
 4.O.236.154; 4.O.236.157; 4.O.236.166; 4.O.236.169; 4.O.236.172; 4.O.236.175;
 4.O.236.240; 4.O.236.244; 4.O.237.228; 4.O.237.229; 4.O.237.230; 4.O.237.231;
 4.O.237.236; 4.O.237.237; 4.O.237.238; 4.O.237.239; 4.O.237.154; 4.O.237.157;
 4.O.237.166; 4.O.237.169; 4.O.237.172; 4.O.237.175; 4.O.237.240; 4.O.237.244;
 30 4.O.238.228; 4.O.238.229; 4.O.238.230; 4.O.238.231; 4.O.238.236; 4.O.238.237;
 4.O.238.238; 4.O.238.239; 4.O.238.154; 4.O.238.157; 4.O.238.166; 4.O.238.169;
 4.O.238.172; 4.O.238.175; 4.O.238.240; 4.O.238.244; 4.O.239.228; 4.O.239.229;
 4.O.239.230; 4.O.239.231; 4.O.239.236; 4.O.239.237; 4.O.239.238; 4.O.239.239;
 4.O.239.154; 4.O.239.157; 4.O.239.166; 4.O.239.169; 4.O.239.172; 4.O.239.175;
 35 4.O.239.240; 4.O.239.244; 4.O.154.228; 4.O.154.229; 4.O.154.230; 4.O.154.231;
 4.O.154.236; 4.O.154.237; 4.O.154.238; 4.O.154.239; 4.O.154.154; 4.O.154.157;
 4.O.154.166; 4.O.154.169; 4.O.154.172; 4.O.154.175; 4.O.154.240; 4.O.154.244;
 4.O.157.228; 4.O.157.229; 4.O.157.230; 4.O.157.231; 4.O.157.236; 4.O.157.237;
 4.O.157.238; 4.O.157.239; 4.O.157.154; 4.O.157.157; 4.O.157.166; 4.O.157.169;
 40 4.O.157.172; 4.O.157.175; 4.O.157.240; 4.O.157.244; 4.O.166.228; 4.O.166.229;
 4.O.166.230; 4.O.166.231; 4.O.166.236; 4.O.166.237; 4.O.166.238; 4.O.166.239;
 4.O.166.154; 4.O.166.157; 4.O.166.166; 4.O.166.169; 4.O.166.172; 4.O.166.175;
 4.O.166.240; 4.O.166.244; 4.O.169.228; 4.O.169.229; 4.O.169.230; 4.O.169.231;
 4.O.169.236; 4.O.169.237; 4.O.169.238; 4.O.169.239; 4.O.169.154; 4.O.169.157;
 45 4.O.169.166; 4.O.169.169; 4.O.169.172; 4.O.169.175; 4.O.169.240; 4.O.169.244;
 4.O.172.228; 4.O.172.229; 4.O.172.230; 4.O.172.231; 4.O.172.236; 4.O.172.237;

4.O.172.238; 4.O.172.239; 4.O.172.154; 4.O.172.157; 4.O.172.166; 4.O.172.169;
 4.O.172.172; 4.O.172.175; 4.O.172.240; 4.O.172.244; 4.O.175.228; 4.O.175.229;
 4.O.175.230; 4.O.175.231; 4.O.175.236; 4.O.175.237; 4.O.175.238; 4.O.175.239;
 4.O.175.154; 4.O.175.157; 4.O.175.166; 4.O.175.169; 4.O.175.172; 4.O.175.175;
 5 4.O.175.240; 4.O.175.244; 4.O.240.228; 4.O.240.229; 4.O.240.230; 4.O.240.231;
 4.O.240.236; 4.O.240.237; 4.O.240.238; 4.O.240.239; 4.O.240.154; 4.O.240.157;
 4.O.240.166; 4.O.240.169; 4.O.240.172; 4.O.240.175; 4.O.240.240; 4.O.240.244;
 4.O.244.228; 4.O.244.229; 4.O.244.230; 4.O.244.231; 4.O.244.236; 4.O.244.237;
 4.O.244.238; 4.O.244.239; 4.O.244.154; 4.O.244.157; 4.O.244.166; 4.O.244.169;
 10 4.O.244.172; 4.O.244.175; 4.O.244.240; 4.O.244.244;

Prodrugs of 4.P

4.P.228.228; 4.P.228.229; 4.P.228.230; 4.P.228.231; 4.P.228.236; 4.P.228.237;
 4.P.228.238; 4.P.228.239; 4.P.228.154; 4.P.228.157; 4.P.228.166; 4.P.228.169; 4.P.228.172;
 15 4.P.228.175; 4.P.228.240; 4.P.228.244; 4.P.229.228; 4.P.229.229; 4.P.229.230; 4.P.229.231;
 4.P.229.236; 4.P.229.237; 4.P.229.238; 4.P.229.239; 4.P.229.154; 4.P.229.157; 4.P.229.166;
 4.P.229.169; 4.P.229.172; 4.P.229.175; 4.P.229.240; 4.P.229.244; 4.P.230.228; 4.P.230.229;
 4.P.230.230; 4.P.230.231; 4.P.230.236; 4.P.230.237; 4.P.230.238; 4.P.230.239; 4.P.230.154;
 4.P.230.157; 4.P.230.166; 4.P.230.169; 4.P.230.172; 4.P.230.175; 4.P.230.240; 4.P.230.244;
 20 4.P.231.228; 4.P.231.229; 4.P.231.230; 4.P.231.231; 4.P.231.236; 4.P.231.237; 4.P.231.238;
 4.P.231.239; 4.P.231.154; 4.P.231.157; 4.P.231.166; 4.P.231.169; 4.P.231.172; 4.P.231.175;
 4.P.231.240; 4.P.231.244; 4.P.236.228; 4.P.236.229; 4.P.236.230; 4.P.236.231; 4.P.236.236;
 4.P.236.237; 4.P.236.238; 4.P.236.239; 4.P.236.154; 4.P.236.157; 4.P.236.166; 4.P.236.169;
 4.P.236.172; 4.P.236.175; 4.P.236.240; 4.P.236.244; 4.P.237.228; 4.P.237.229; 4.P.237.230;
 25 4.P.237.231; 4.P.237.236; 4.P.237.237; 4.P.237.238; 4.P.237.239; 4.P.237.154; 4.P.237.157;
 4.P.237.166; 4.P.237.169; 4.P.237.172; 4.P.237.175; 4.P.237.240; 4.P.237.244; 4.P.238.228;
 4.P.238.229; 4.P.238.230; 4.P.238.231; 4.P.238.236; 4.P.238.237; 4.P.238.238; 4.P.238.239;
 4.P.238.154; 4.P.238.157; 4.P.238.166; 4.P.238.169; 4.P.238.172; 4.P.238.175; 4.P.238.240;
 4.P.238.244; 4.P.239.228; 4.P.239.229; 4.P.239.230; 4.P.239.231; 4.P.239.236; 4.P.239.237;
 30 4.P.239.238; 4.P.239.239; 4.P.239.154; 4.P.239.157; 4.P.239.166; 4.P.239.169; 4.P.239.172;
 4.P.239.175; 4.P.239.240; 4.P.239.244; 4.P.154.228; 4.P.154.229; 4.P.154.230; 4.P.154.231;
 4.P.154.236; 4.P.154.237; 4.P.154.238; 4.P.154.239; 4.P.154.154; 4.P.154.157; 4.P.154.166;
 4.P.154.169; 4.P.154.172; 4.P.154.175; 4.P.154.240; 4.P.154.244; 4.P.157.228; 4.P.157.229;
 4.P.157.230; 4.P.157.231; 4.P.157.236; 4.P.157.237; 4.P.157.238; 4.P.157.239; 4.P.157.154;
 35 4.P.157.157; 4.P.157.166; 4.P.157.169; 4.P.157.172; 4.P.157.175; 4.P.157.240; 4.P.157.244;
 4.P.166.228; 4.P.166.229; 4.P.166.230; 4.P.166.231; 4.P.166.236; 4.P.166.237; 4.P.166.238;
 4.P.166.239; 4.P.166.154; 4.P.166.157; 4.P.166.166; 4.P.166.169; 4.P.166.172; 4.P.166.175;
 4.P.166.240; 4.P.166.244; 4.P.169.228; 4.P.169.229; 4.P.169.230; 4.P.169.231; 4.P.169.236;
 4.P.169.237; 4.P.169.238; 4.P.169.239; 4.P.169.154; 4.P.169.157; 4.P.169.166; 4.P.169.169;
 40 4.P.169.172; 4.P.169.175; 4.P.169.240; 4.P.169.244; 4.P.172.228; 4.P.172.229; 4.P.172.230;
 4.P.172.231; 4.P.172.236; 4.P.172.237; 4.P.172.238; 4.P.172.239; 4.P.172.154; 4.P.172.157;
 4.P.172.166; 4.P.172.169; 4.P.172.172; 4.P.172.175; 4.P.172.240; 4.P.172.244; 4.P.175.228;
 4.P.175.229; 4.P.175.230; 4.P.175.231; 4.P.175.236; 4.P.175.237; 4.P.175.238; 4.P.175.239;
 4.P.175.154; 4.P.175.157; 4.P.175.166; 4.P.175.169; 4.P.175.172; 4.P.175.175; 4.P.175.240;
 45 4.P.175.244; 4.P.240.228; 4.P.240.229; 4.P.240.230; 4.P.240.231; 4.P.240.236; 4.P.240.237;
 4.P.240.238; 4.P.240.239; 4.P.240.154; 4.P.240.157; 4.P.240.166; 4.P.240.169; 4.P.240.172;

4.P.240.175; 4.P.240.240; 4.P.240.244; 4.P.244.228; 4.P.244.229; 4.P.244.230; 4.P.244.231;
 4.P.244.236; 4.P.244.237; 4.P.244.238; 4.P.244.239; 4.P.244.154; 4.P.244.157; 4.P.244.166;
 4.P.244.169; 4.P.244.172; 4.P.244.175; 4.P.244.240; 4.P.244.244;

5 Prodrugs of 4.U

- 4.U.228.228; 4.U.228.229; 4.U.228.230; 4.U.228.231; 4.U.228.236; 4.U.228.237;
 4.U.228.238; 4.U.228.239; 4.U.228.154; 4.U.228.157; 4.U.228.166; 4.U.228.169;
 4.U.228.172; 4.U.228.175; 4.U.228.240; 4.U.228.244; 4.U.229.228; 4.U.229.229;
 4.U.229.230; 4.U.229.231; 4.U.229.236; 4.U.229.237; 4.U.229.238; 4.U.229.239;
 10 4.U.229.154; 4.U.229.157; 4.U.229.166; 4.U.229.169; 4.U.229.172; 4.U.229.175;
 4.U.229.240; 4.U.229.244; 4.U.230.228; 4.U.230.229; 4.U.230.230; 4.U.230.231;
 4.U.230.236; 4.U.230.237; 4.U.230.238; 4.U.230.239; 4.U.230.154; 4.U.230.157;
 4.U.230.166; 4.U.230.169; 4.U.230.172; 4.U.230.175; 4.U.230.240; 4.U.230.244;
 4.U.231.228; 4.U.231.229; 4.U.231.230; 4.U.231.231; 4.U.231.236; 4.U.231.237;
 15 4.U.231.238; 4.U.231.239; 4.U.231.154; 4.U.231.157; 4.U.231.166; 4.U.231.169;
 4.U.231.172; 4.U.231.175; 4.U.231.240; 4.U.231.244; 4.U.236.228; 4.U.236.229;
 4.U.236.230; 4.U.236.231; 4.U.236.236; 4.U.236.237; 4.U.236.238; 4.U.236.239;
 4.U.236.154; 4.U.236.157; 4.U.236.166; 4.U.236.169; 4.U.236.172; 4.U.236.175;
 4.U.236.240; 4.U.236.244; 4.U.237.228; 4.U.237.229; 4.U.237.230; 4.U.237.231;
 20 4.U.237.236; 4.U.237.237; 4.U.237.238; 4.U.237.239; 4.U.237.154; 4.U.237.157;
 4.U.237.166; 4.U.237.169; 4.U.237.172; 4.U.237.175; 4.U.237.240; 4.U.237.244;
 4.U.238.228; 4.U.238.229; 4.U.238.230; 4.U.238.231; 4.U.238.236; 4.U.238.237;
 4.U.238.238; 4.U.238.239; 4.U.238.154; 4.U.238.157; 4.U.238.166; 4.U.238.169;
 4.U.238.172; 4.U.238.175; 4.U.238.240; 4.U.238.244; 4.U.239.228; 4.U.239.229;
 25 4.U.239.230; 4.U.239.231; 4.U.239.236; 4.U.239.237; 4.U.239.238; 4.U.239.239;
 4.U.239.154; 4.U.239.157; 4.U.239.166; 4.U.239.169; 4.U.239.172; 4.U.239.175;
 4.U.239.240; 4.U.239.244; 4.U.154.228; 4.U.154.229; 4.U.154.230; 4.U.154.231;
 4.U.154.236; 4.U.154.237; 4.U.154.238; 4.U.154.239; 4.U.154.154; 4.U.154.157;
 4.U.154.166; 4.U.154.169; 4.U.154.172; 4.U.154.175; 4.U.154.240; 4.U.154.244;
 30 4.U.157.228; 4.U.157.229; 4.U.157.230; 4.U.157.231; 4.U.157.236; 4.U.157.237;
 4.U.157.238; 4.U.157.239; 4.U.157.154; 4.U.157.157; 4.U.157.166; 4.U.157.169;
 4.U.157.172; 4.U.157.175; 4.U.157.240; 4.U.157.244; 4.U.166.228; 4.U.166.229;
 4.U.166.230; 4.U.166.231; 4.U.166.236; 4.U.166.237; 4.U.166.238; 4.U.166.239;
 4.U.166.154; 4.U.166.157; 4.U.166.166; 4.U.166.169; 4.U.166.172; 4.U.166.175;
 35 4.U.166.240; 4.U.166.244; 4.U.169.228; 4.U.169.229; 4.U.169.230; 4.U.169.231;
 4.U.169.236; 4.U.169.237; 4.U.169.238; 4.U.169.239; 4.U.169.154; 4.U.169.157;
 4.U.169.166; 4.U.169.169; 4.U.169.172; 4.U.169.175; 4.U.169.240; 4.U.169.244;
 4.U.172.228; 4.U.172.229; 4.U.172.230; 4.U.172.231; 4.U.172.236; 4.U.172.237;
 4.U.172.238; 4.U.172.239; 4.U.172.154; 4.U.172.157; 4.U.172.166; 4.U.172.169;
 40 4.U.172.172; 4.U.172.175; 4.U.172.240; 4.U.172.244; 4.U.175.228; 4.U.175.229;
 4.U.175.230; 4.U.175.231; 4.U.175.236; 4.U.175.237; 4.U.175.238; 4.U.175.239;
 4.U.175.154; 4.U.175.157; 4.U.175.166; 4.U.175.169; 4.U.175.172; 4.U.175.175;
 4.U.175.240; 4.U.175.244; 4.U.240.228; 4.U.240.229; 4.U.240.230; 4.U.240.231;
 4.U.240.236; 4.U.240.237; 4.U.240.238; 4.U.240.239; 4.U.240.154; 4.U.240.157;
 45 4.U.240.166; 4.U.240.169; 4.U.240.172; 4.U.240.175; 4.U.240.240; 4.U.240.244;
 4.U.244.228; 4.U.244.229; 4.U.244.230; 4.U.244.231; 4.U.244.236; 4.U.244.237;

4.U.244.238; 4.U.244.239; 4.U.244.154; 4.U.244.157; 4.U.244.166; 4.U.244.169;
4.U.244.172; 4.U.244.175; 4.U.244.240; 4.U.244.244;

Prodrugs of 4.W

- 5 4.W.228.228; 4.W.228.229; 4.W.228.230; 4.W.228.231; 4.W.228.236; 4.W.228.237;
4.W.228.238; 4.W.228.239; 4.W.228.154; 4.W.228.157; 4.W.228.166; 4.W.228.169;
4.W.228.172; 4.W.228.175; 4.W.228.240; 4.W.228.244; 4.W.229.228; 4.W.229.229;
4.W.229.230; 4.W.229.231; 4.W.229.236; 4.W.229.237; 4.W.229.238; 4.W.229.239;
4.W.229.154; 4.W.229.157; 4.W.229.166; 4.W.229.169; 4.W.229.172; 4.W.229.175;
10 4.W.229.240; 4.W.229.244; 4.W.230.228; 4.W.230.229; 4.W.230.230; 4.W.230.231;
4.W.230.236; 4.W.230.237; 4.W.230.238; 4.W.230.239; 4.W.230.154; 4.W.230.157;
4.W.230.166; 4.W.230.169; 4.W.230.172; 4.W.230.175; 4.W.230.240; 4.W.230.244;
4.W.231.228; 4.W.231.229; 4.W.231.230; 4.W.231.231; 4.W.231.236; 4.W.231.237;
4.W.231.238; 4.W.231.239; 4.W.231.154; 4.W.231.157; 4.W.231.166; 4.W.231.169;
15 4.W.231.172; 4.W.231.175; 4.W.231.240; 4.W.231.244; 4.W.236.228; 4.W.236.229;
4.W.236.230; 4.W.236.231; 4.W.236.236; 4.W.236.237; 4.W.236.238; 4.W.236.239;
4.W.236.154; 4.W.236.157; 4.W.236.166; 4.W.236.169; 4.W.236.172; 4.W.236.175;
4.W.236.240; 4.W.236.244; 4.W.237.228; 4.W.237.229; 4.W.237.230; 4.W.237.231;
4.W.237.236; 4.W.237.237; 4.W.237.238; 4.W.237.239; 4.W.237.154; 4.W.237.157;
20 4.W.237.166; 4.W.237.169; 4.W.237.172; 4.W.237.175; 4.W.237.240; 4.W.237.244;
4.W.238.228; 4.W.238.229; 4.W.238.230; 4.W.238.231; 4.W.238.236; 4.W.238.237;
4.W.238.238; 4.W.238.239; 4.W.238.154; 4.W.238.157; 4.W.238.166; 4.W.238.169;
4.W.238.172; 4.W.238.175; 4.W.238.240; 4.W.238.244; 4.W.239.228; 4.W.239.229;
4.W.239.230; 4.W.239.231; 4.W.239.236; 4.W.239.237; 4.W.239.238; 4.W.239.239;
25 4.W.239.154; 4.W.239.157; 4.W.239.166; 4.W.239.169; 4.W.239.172; 4.W.239.175;
4.W.239.240; 4.W.239.244; 4.W.154.228; 4.W.154.229; 4.W.154.230; 4.W.154.231;
4.W.154.236; 4.W.154.237; 4.W.154.238; 4.W.154.239; 4.W.154.154; 4.W.154.157;
4.W.154.166; 4.W.154.169; 4.W.154.172; 4.W.154.175; 4.W.154.240; 4.W.154.244;
4.W.157.228; 4.W.157.229; 4.W.157.230; 4.W.157.231; 4.W.157.236; 4.W.157.237;
30 4.W.157.238; 4.W.157.239; 4.W.157.154; 4.W.157.157; 4.W.157.166; 4.W.157.169;
4.W.157.172; 4.W.157.175; 4.W.157.240; 4.W.157.244; 4.W.166.228; 4.W.166.229;
4.W.166.230; 4.W.166.231; 4.W.166.236; 4.W.166.237; 4.W.166.238; 4.W.166.239;
4.W.166.154; 4.W.166.157; 4.W.166.166; 4.W.166.169; 4.W.166.172; 4.W.166.175;
4.W.166.240; 4.W.166.244; 4.W.169.228; 4.W.169.229; 4.W.169.230; 4.W.169.231;
35 4.W.169.236; 4.W.169.237; 4.W.169.238; 4.W.169.239; 4.W.169.154; 4.W.169.157;
4.W.169.166; 4.W.169.169; 4.W.169.172; 4.W.169.175; 4.W.169.240; 4.W.169.244;
4.W.172.228; 4.W.172.229; 4.W.172.230; 4.W.172.231; 4.W.172.236; 4.W.172.237;
4.W.172.238; 4.W.172.239; 4.W.172.154; 4.W.172.157; 4.W.172.166; 4.W.172.169;
4.W.172.172; 4.W.172.175; 4.W.172.240; 4.W.172.244; 4.W.175.228; 4.W.175.229;
40 4.W.175.230; 4.W.175.231; 4.W.175.236; 4.W.175.237; 4.W.175.238; 4.W.175.239;
4.W.175.154; 4.W.175.157; 4.W.175.166; 4.W.175.169; 4.W.175.172; 4.W.175.175;
4.W.175.240; 4.W.175.244; 4.W.240.228; 4.W.240.229; 4.W.240.230; 4.W.240.231;
4.W.240.236; 4.W.240.237; 4.W.240.238; 4.W.240.239; 4.W.240.154; 4.W.240.157;
4.W.240.166; 4.W.240.169; 4.W.240.172; 4.W.240.175; 4.W.240.240; 4.W.240.244;
45 4.W.244.228; 4.W.244.229; 4.W.244.230; 4.W.244.231; 4.W.244.236; 4.W.244.237;

4.W.244.238; 4.W.244.239; 4.W.244.154; 4.W.244.157; 4.W.244.166; 4.W.244.169;
4.W.244.172; 4.W.244.175; 4.W.244.240; 4.W.244.244;

Prodrugs of 4.Y

- 5 4.Y.228.228; 4.Y.228.229; 4.Y.228.230; 4.Y.228.231; 4.Y.228.236; 4.Y.228.237;
4.Y.228.238; 4.Y.228.239; 4.Y.228.154; 4.Y.228.157; 4.Y.228.166; 4.Y.228.169;
4.Y.228.172; 4.Y.228.175; 4.Y.228.240; 4.Y.228.244; 4.Y.229.228; 4.Y.229.229;
4.Y.229.230; 4.Y.229.231; 4.Y.229.236; 4.Y.229.237; 4.Y.229.238; 4.Y.229.239;
4.Y.229.154; 4.Y.229.157; 4.Y.229.166; 4.Y.229.169; 4.Y.229.172; 4.Y.229.175;
10 4.Y.229.240; 4.Y.229.244; 4.Y.230.228; 4.Y.230.229; 4.Y.230.230; 4.Y.230.231;
4.Y.230.236; 4.Y.230.237; 4.Y.230.238; 4.Y.230.239; 4.Y.230.154; 4.Y.230.157;
4.Y.230.166; 4.Y.230.169; 4.Y.230.172; 4.Y.230.175; 4.Y.230.240; 4.Y.230.244;
4.Y.231.228; 4.Y.231.229; 4.Y.231.230; 4.Y.231.231; 4.Y.231.236; 4.Y.231.237;
4.Y.231.238; 4.Y.231.239; 4.Y.231.154; 4.Y.231.157; 4.Y.231.166; 4.Y.231.169;
15 4.Y.231.172; 4.Y.231.175; 4.Y.231.240; 4.Y.231.244; 4.Y.236.228; 4.Y.236.229;
4.Y.236.230; 4.Y.236.231; 4.Y.236.236; 4.Y.236.237; 4.Y.236.238; 4.Y.236.239;
4.Y.236.154; 4.Y.236.157; 4.Y.236.166; 4.Y.236.169; 4.Y.236.172; 4.Y.236.175;
4.Y.236.240; 4.Y.236.244; 4.Y.237.228; 4.Y.237.229; 4.Y.237.230; 4.Y.237.231;
4.Y.237.236; 4.Y.237.237; 4.Y.237.238; 4.Y.237.239; 4.Y.237.154; 4.Y.237.157;
20 4.Y.237.166; 4.Y.237.169; 4.Y.237.172; 4.Y.237.175; 4.Y.237.240; 4.Y.237.244;
4.Y.238.228; 4.Y.238.229; 4.Y.238.230; 4.Y.238.231; 4.Y.238.236; 4.Y.238.237;
4.Y.238.238; 4.Y.238.239; 4.Y.238.154; 4.Y.238.157; 4.Y.238.166; 4.Y.238.169;
4.Y.238.172; 4.Y.238.175; 4.Y.238.240; 4.Y.238.244; 4.Y.239.228; 4.Y.239.229;
4.Y.239.230; 4.Y.239.231; 4.Y.239.236; 4.Y.239.237; 4.Y.239.238; 4.Y.239.239;
25 4.Y.239.154; 4.Y.239.157; 4.Y.239.166; 4.Y.239.169; 4.Y.239.172; 4.Y.239.175;
4.Y.239.240; 4.Y.239.244; 4.Y.154.228; 4.Y.154.229; 4.Y.154.230; 4.Y.154.231;
4.Y.154.236; 4.Y.154.237; 4.Y.154.238; 4.Y.154.239; 4.Y.154.154; 4.Y.154.157;
4.Y.154.166; 4.Y.154.169; 4.Y.154.172; 4.Y.154.175; 4.Y.154.240; 4.Y.154.244;
4.Y.157.228; 4.Y.157.229; 4.Y.157.230; 4.Y.157.231; 4.Y.157.236; 4.Y.157.237;
30 4.Y.157.238; 4.Y.157.239; 4.Y.157.154; 4.Y.157.157; 4.Y.157.166; 4.Y.157.169;
4.Y.157.172; 4.Y.157.175; 4.Y.157.240; 4.Y.157.244; 4.Y.166.228; 4.Y.166.229;
4.Y.166.230; 4.Y.166.231; 4.Y.166.236; 4.Y.166.237; 4.Y.166.238; 4.Y.166.239;
4.Y.166.154; 4.Y.166.157; 4.Y.166.166; 4.Y.166.169; 4.Y.166.172; 4.Y.166.175;
4.Y.166.240; 4.Y.166.244; 4.Y.169.228; 4.Y.169.229; 4.Y.169.230; 4.Y.169.231;
35 4.Y.169.236; 4.Y.169.237; 4.Y.169.238; 4.Y.169.239; 4.Y.169.154; 4.Y.169.157;
4.Y.169.166; 4.Y.169.169; 4.Y.169.172; 4.Y.169.175; 4.Y.169.240; 4.Y.169.244;
4.Y.172.228; 4.Y.172.229; 4.Y.172.230; 4.Y.172.231; 4.Y.172.236; 4.Y.172.237;
4.Y.172.238; 4.Y.172.239; 4.Y.172.154; 4.Y.172.157; 4.Y.172.166; 4.Y.172.169;
4.Y.172.172; 4.Y.172.175; 4.Y.172.240; 4.Y.172.244; 4.Y.175.228; 4.Y.175.229;
40 4.Y.175.230; 4.Y.175.231; 4.Y.175.236; 4.Y.175.237; 4.Y.175.238; 4.Y.175.239;
4.Y.175.154; 4.Y.175.157; 4.Y.175.166; 4.Y.175.169; 4.Y.175.172; 4.Y.175.175;
4.Y.175.240; 4.Y.175.244; 4.Y.240.228; 4.Y.240.229; 4.Y.240.230; 4.Y.240.231;
4.Y.240.236; 4.Y.240.237; 4.Y.240.238; 4.Y.240.239; 4.Y.240.154; 4.Y.240.157;
4.Y.240.166; 4.Y.240.169; 4.Y.240.172; 4.Y.240.175; 4.Y.240.240; 4.Y.240.244;
45 4.Y.244.228; 4.Y.244.229; 4.Y.244.230; 4.Y.244.231; 4.Y.244.236; 4.Y.244.237;

4.Y.244.238; 4.Y.244.239; 4.Y.244.154; 4.Y.244.157; 4.Y.244.166; 4.Y.244.169;
4.Y.244.172; 4.Y.244.175; 4.Y.244.240; 4.Y.244.244;

Prodrugs of 5.B

- 5 5.B.228.228; 5.B.228.229; 5.B.228.230; 5.B.228.231; 5.B.228.236; 5.B.228.237;
5.B.228.238; 5.B.228.239; 5.B.228.154; 5.B.228.157; 5.B.228.166; 5.B.228.169; 5.B.228.172;
5.B.228.175; 5.B.228.240; 5.B.228.244; 5.B.229.228; 5.B.229.229; 5.B.229.230; 5.B.229.231;
5.B.229.236; 5.B.229.237; 5.B.229.238; 5.B.229.239; 5.B.229.154; 5.B.229.157; 5.B.229.166;
5.B.229.169; 5.B.229.172; 5.B.229.175; 5.B.229.240; 5.B.229.244; 5.B.230.228; 5.B.230.229;
10 5.B.230.230; 5.B.230.231; 5.B.230.236; 5.B.230.237; 5.B.230.238; 5.B.230.239; 5.B.230.154;
5.B.230.157; 5.B.230.166; 5.B.230.169; 5.B.230.172; 5.B.230.175; 5.B.230.240; 5.B.230.244;
5.B.231.228; 5.B.231.229; 5.B.231.230; 5.B.231.231; 5.B.231.236; 5.B.231.237; 5.B.231.238;
5.B.231.239; 5.B.231.154; 5.B.231.157; 5.B.231.166; 5.B.231.169; 5.B.231.172; 5.B.231.175;
5.B.231.240; 5.B.231.244; 5.B.236.228; 5.B.236.229; 5.B.236.230; 5.B.236.231; 5.B.236.236;
15 5.B.236.237; 5.B.236.238; 5.B.236.239; 5.B.236.154; 5.B.236.157; 5.B.236.166; 5.B.236.169;
5.B.236.172; 5.B.236.175; 5.B.236.240; 5.B.236.244; 5.B.237.228; 5.B.237.229; 5.B.237.230;
5.B.237.231; 5.B.237.236; 5.B.237.237; 5.B.237.238; 5.B.237.239; 5.B.237.154; 5.B.237.157;
5.B.237.166; 5.B.237.169; 5.B.237.172; 5.B.237.175; 5.B.237.240; 5.B.237.244; 5.B.238.228;
5.B.238.229; 5.B.238.230; 5.B.238.231; 5.B.238.236; 5.B.238.237; 5.B.238.238; 5.B.238.239;
20 5.B.238.154; 5.B.238.157; 5.B.238.166; 5.B.238.169; 5.B.238.172; 5.B.238.175; 5.B.238.240;
5.B.238.244; 5.B.239.228; 5.B.239.229; 5.B.239.230; 5.B.239.231; 5.B.239.236; 5.B.239.237;
5.B.239.238; 5.B.239.239; 5.B.239.154; 5.B.239.157; 5.B.239.166; 5.B.239.169; 5.B.239.172;
5.B.239.175; 5.B.239.240; 5.B.239.244; 5.B.154.228; 5.B.154.229; 5.B.154.230; 5.B.154.231;
5.B.154.236; 5.B.154.237; 5.B.154.238; 5.B.154.239; 5.B.154.154; 5.B.154.157; 5.B.154.166;
25 5.B.154.169; 5.B.154.172; 5.B.154.175; 5.B.154.240; 5.B.154.244; 5.B.157.228; 5.B.157.229;
5.B.157.230; 5.B.157.231; 5.B.157.236; 5.B.157.237; 5.B.157.238; 5.B.157.239; 5.B.157.154;
5.B.157.157; 5.B.157.166; 5.B.157.169; 5.B.157.172; 5.B.157.175; 5.B.157.240; 5.B.157.244;
5.B.166.228; 5.B.166.229; 5.B.166.230; 5.B.166.231; 5.B.166.236; 5.B.166.237; 5.B.166.238;
5.B.166.239; 5.B.166.154; 5.B.166.157; 5.B.166.166; 5.B.166.169; 5.B.166.172; 5.B.166.175;
30 5.B.166.240; 5.B.166.244; 5.B.169.228; 5.B.169.229; 5.B.169.230; 5.B.169.231; 5.B.169.236;
5.B.169.237; 5.B.169.238; 5.B.169.239; 5.B.169.154; 5.B.169.157; 5.B.169.166; 5.B.169.169;
5.B.169.172; 5.B.169.175; 5.B.169.240; 5.B.169.244; 5.B.172.228; 5.B.172.229; 5.B.172.230;
5.B.172.231; 5.B.172.236; 5.B.172.237; 5.B.172.238; 5.B.172.239; 5.B.172.154; 5.B.172.157;
5.B.172.166; 5.B.172.169; 5.B.172.172; 5.B.172.175; 5.B.172.240; 5.B.172.244; 5.B.175.228;
35 5.B.175.229; 5.B.175.230; 5.B.175.231; 5.B.175.236; 5.B.175.237; 5.B.175.238; 5.B.175.239;
5.B.175.154; 5.B.175.157; 5.B.175.166; 5.B.175.169; 5.B.175.172; 5.B.175.175; 5.B.175.240;
5.B.175.244; 5.B.240.228; 5.B.240.229; 5.B.240.230; 5.B.240.231; 5.B.240.236; 5.B.240.237;
5.B.240.238; 5.B.240.239; 5.B.240.154; 5.B.240.157; 5.B.240.166; 5.B.240.169; 5.B.240.172;
5.B.240.175; 5.B.240.240; 5.B.240.244; 5.B.244.228; 5.B.244.229; 5.B.244.230; 5.B.244.231;
40 5.B.244.236; 5.B.244.237; 5.B.244.238; 5.B.244.239; 5.B.244.154; 5.B.244.157; 5.B.244.166;
5.B.244.169; 5.B.244.172; 5.B.244.175; 5.B.244.240; 5.B.244.244;

Prodrugs of 5.D

- 5.D.228.228; 5.D.228.229; 5.D.228.230; 5.D.228.231; 5.D.228.236; 5.D.228.237;
45 5.D.228.238; 5.D.228.239; 5.D.228.154; 5.D.228.157; 5.D.228.166; 5.D.228.169;
5.D.228.172; 5.D.228.175; 5.D.228.240; 5.D.228.244; 5.D.229.228; 5.D.229.229;

5.D.229.230; 5.D.229.231; 5.D.229.236; 5.D.229.237; 5.D.229.238; 5.D.229.239;
 5.D.229.154; 5.D.229.157; 5.D.229.166; 5.D.229.169; 5.D.229.172; 5.D.229.175;
 5.D.229.240; 5.D.229.244; 5.D.230.228; 5.D.230.229; 5.D.230.230; 5.D.230.231;
 5.D.230.236; 5.D.230.237; 5.D.230.238; 5.D.230.239; 5.D.230.154; 5.D.230.157;
 5 5.D.230.166; 5.D.230.169; 5.D.230.172; 5.D.230.175; 5.D.230.240; 5.D.230.244;
 5.D.231.228; 5.D.231.229; 5.D.231.230; 5.D.231.231; 5.D.231.236; 5.D.231.237;
 5.D.231.238; 5.D.231.239; 5.D.231.154; 5.D.231.157; 5.D.231.166; 5.D.231.169;
 5.D.231.172; 5.D.231.175; 5.D.231.240; 5.D.231.244; 5.D.236.228; 5.D.236.229;
 5.D.236.230; 5.D.236.231; 5.D.236.236; 5.D.236.237; 5.D.236.238; 5.D.236.239;
 10 5.D.236.154; 5.D.236.157; 5.D.236.166; 5.D.236.169; 5.D.236.172; 5.D.236.175;
 5.D.236.240; 5.D.236.244; 5.D.237.228; 5.D.237.229; 5.D.237.230; 5.D.237.231;
 5.D.237.236; 5.D.237.237; 5.D.237.238; 5.D.237.239; 5.D.237.154; 5.D.237.157;
 5.D.237.166; 5.D.237.169; 5.D.237.172; 5.D.237.175; 5.D.237.240; 5.D.237.244;
 5.D.238.228; 5.D.238.229; 5.D.238.230; 5.D.238.231; 5.D.238.236; 5.D.238.237;
 15 5.D.238.238; 5.D.238.239; 5.D.238.154; 5.D.238.157; 5.D.238.166; 5.D.238.169;
 5.D.238.172; 5.D.238.175; 5.D.238.240; 5.D.238.244; 5.D.239.228; 5.D.239.229;
 5.D.239.230; 5.D.239.231; 5.D.239.236; 5.D.239.237; 5.D.239.238; 5.D.239.239;
 5.D.239.154; 5.D.239.157; 5.D.239.166; 5.D.239.169; 5.D.239.172; 5.D.239.175;
 5.D.239.240; 5.D.239.244; 5.D.154.228; 5.D.154.229; 5.D.154.230; 5.D.154.231;
 20 5.D.154.236; 5.D.154.237; 5.D.154.238; 5.D.154.239; 5.D.154.154; 5.D.154.157;
 5.D.154.166; 5.D.154.169; 5.D.154.172; 5.D.154.175; 5.D.154.240; 5.D.154.244;
 5.D.157.228; 5.D.157.229; 5.D.157.230; 5.D.157.231; 5.D.157.236; 5.D.157.237;
 5.D.157.238; 5.D.157.239; 5.D.157.154; 5.D.157.157; 5.D.157.166; 5.D.157.169;
 5.D.157.172; 5.D.157.175; 5.D.157.240; 5.D.157.244; 5.D.166.228; 5.D.166.229;
 25 5.D.166.230; 5.D.166.231; 5.D.166.236; 5.D.166.237; 5.D.166.238; 5.D.166.239;
 5.D.166.154; 5.D.166.157; 5.D.166.166; 5.D.166.169; 5.D.166.172; 5.D.166.175;
 5.D.166.240; 5.D.166.244; 5.D.169.228; 5.D.169.229; 5.D.169.230; 5.D.169.231;
 5.D.169.236; 5.D.169.237; 5.D.169.238; 5.D.169.239; 5.D.169.154; 5.D.169.157;
 5.D.169.166; 5.D.169.169; 5.D.169.172; 5.D.169.175; 5.D.169.240; 5.D.169.244;
 30 5.D.172.228; 5.D.172.229; 5.D.172.230; 5.D.172.231; 5.D.172.236; 5.D.172.237;
 5.D.172.238; 5.D.172.239; 5.D.172.154; 5.D.172.157; 5.D.172.166; 5.D.172.169;
 5.D.172.172; 5.D.172.175; 5.D.172.240; 5.D.172.244; 5.D.175.228; 5.D.175.229;
 5.D.175.230; 5.D.175.231; 5.D.175.236; 5.D.175.237; 5.D.175.238; 5.D.175.239;
 5.D.175.154; 5.D.175.157; 5.D.175.166; 5.D.175.169; 5.D.175.172; 5.D.175.175;
 35 5.D.175.240; 5.D.175.244; 5.D.240.228; 5.D.240.229; 5.D.240.230; 5.D.240.231;
 5.D.240.236; 5.D.240.237; 5.D.240.238; 5.D.240.239; 5.D.240.154; 5.D.240.157;
 5.D.240.166; 5.D.240.169; 5.D.240.172; 5.D.240.175; 5.D.240.240; 5.D.240.244;
 5.D.244.228; 5.D.244.229; 5.D.244.230; 5.D.244.231; 5.D.244.236; 5.D.244.237;
 5.D.244.238; 5.D.244.239; 5.D.244.154; 5.D.244.157; 5.D.244.166; 5.D.244.169;
 40 5.D.244.172; 5.D.244.175; 5.D.244.240; 5.D.244.244;

Prodrugs of 5.E

5.E.228.228; 5.E.228.229; 5.E.228.230; 5.E.228.231; 5.E.228.236; 5.E.228.237;
 5.E.228.238; 5.E.228.239; 5.E.228.154; 5.E.228.157; 5.E.228.166; 5.E.228.169; 5.E.228.172;
 45 5.E.228.175; 5.E.228.240; 5.E.228.244; 5.E.229.228; 5.E.229.229; 5.E.229.230; 5.E.229.231;
 5.E.229.236; 5.E.229.237; 5.E.229.238; 5.E.229.239; 5.E.229.154; 5.E.229.157; 5.E.229.166;

5.E.229.169; 5.E.229.172; 5.E.229.175; 5.E.229.240; 5.E.229.244; 5.E.230.228; 5.E.230.229;
 5.E.230.230; 5.E.230.231; 5.E.230.236; 5.E.230.237; 5.E.230.238; 5.E.230.239; 5.E.230.154;
 5.E.230.157; 5.E.230.166; 5.E.230.169; 5.E.230.172; 5.E.230.175; 5.E.230.240; 5.E.230.244;
 5.E.231.228; 5.E.231.229; 5.E.231.230; 5.E.231.231; 5.E.231.236; 5.E.231.237; 5.E.231.238;
 5 5.E.231.239; 5.E.231.154; 5.E.231.157; 5.E.231.166; 5.E.231.169; 5.E.231.172; 5.E.231.175;
 5.E.231.240; 5.E.231.244; 5.E.236.228; 5.E.236.229; 5.E.236.230; 5.E.236.231; 5.E.236.236;
 5.E.236.237; 5.E.236.238; 5.E.236.239; 5.E.236.154; 5.E.236.157; 5.E.236.166; 5.E.236.169;
 5.E.236.172; 5.E.236.175; 5.E.236.240; 5.E.236.244; 5.E.237.228; 5.E.237.229; 5.E.237.230;
 5.E.237.231; 5.E.237.236; 5.E.237.237; 5.E.237.238; 5.E.237.239; 5.E.237.154; 5.E.237.157;
 10 5.E.237.166; 5.E.237.169; 5.E.237.172; 5.E.237.175; 5.E.237.240; 5.E.237.244; 5.E.238.228;
 5.E.238.229; 5.E.238.230; 5.E.238.231; 5.E.238.236; 5.E.238.237; 5.E.238.238; 5.E.238.239;
 5.E.238.154; 5.E.238.157; 5.E.238.166; 5.E.238.169; 5.E.238.172; 5.E.238.175; 5.E.238.240;
 5.E.238.244; 5.E.239.228; 5.E.239.229; 5.E.239.230; 5.E.239.231; 5.E.239.236; 5.E.239.237;
 5.E.239.238; 5.E.239.239; 5.E.239.154; 5.E.239.157; 5.E.239.166; 5.E.239.169; 5.E.239.172;
 15 5.E.239.175; 5.E.239.240; 5.E.239.244; 5.E.154.228; 5.E.154.229; 5.E.154.230; 5.E.154.231;
 5.E.154.236; 5.E.154.237; 5.E.154.238; 5.E.154.239; 5.E.154.154; 5.E.154.157; 5.E.154.166;
 5.E.154.169; 5.E.154.172; 5.E.154.175; 5.E.154.240; 5.E.154.244; 5.E.157.228; 5.E.157.229;
 5.E.157.230; 5.E.157.231; 5.E.157.236; 5.E.157.237; 5.E.157.238; 5.E.157.239; 5.E.157.154;
 5.E.157.157; 5.E.157.166; 5.E.157.169; 5.E.157.172; 5.E.157.175; 5.E.157.240; 5.E.157.244;
 20 5.E.166.228; 5.E.166.229; 5.E.166.230; 5.E.166.231; 5.E.166.236; 5.E.166.237; 5.E.166.238;
 5.E.166.239; 5.E.166.154; 5.E.166.157; 5.E.166.166; 5.E.166.169; 5.E.166.172; 5.E.166.175;
 5.E.166.240; 5.E.166.244; 5.E.169.228; 5.E.169.229; 5.E.169.230; 5.E.169.231; 5.E.169.236;
 5.E.169.237; 5.E.169.238; 5.E.169.239; 5.E.169.154; 5.E.169.157; 5.E.169.166; 5.E.169.169;
 5.E.169.172; 5.E.169.175; 5.E.169.240; 5.E.169.244; 5.E.172.228; 5.E.172.229; 5.E.172.230;
 25 5.E.172.231; 5.E.172.236; 5.E.172.237; 5.E.172.238; 5.E.172.239; 5.E.172.154; 5.E.172.157;
 5.E.172.166; 5.E.172.169; 5.E.172.172; 5.E.172.175; 5.E.172.240; 5.E.172.244; 5.E.175.228;
 5.E.175.229; 5.E.175.230; 5.E.175.231; 5.E.175.236; 5.E.175.237; 5.E.175.238; 5.E.175.239;
 5.E.175.154; 5.E.175.157; 5.E.175.166; 5.E.175.169; 5.E.175.172; 5.E.175.175; 5.E.175.240;
 5.E.175.244; 5.E.240.228; 5.E.240.229; 5.E.240.230; 5.E.240.231; 5.E.240.236; 5.E.240.237;
 30 5.E.240.238; 5.E.240.239; 5.E.240.154; 5.E.240.157; 5.E.240.166; 5.E.240.169; 5.E.240.172;
 5.E.240.175; 5.E.240.240; 5.E.240.244; 5.E.244.228; 5.E.244.229; 5.E.244.230; 5.E.244.231;
 5.E.244.236; 5.E.244.237; 5.E.244.238; 5.E.244.239; 5.E.244.154; 5.E.244.157; 5.E.244.166;
 5.E.244.169; 5.E.244.172; 5.E.244.175; 5.E.244.240; 5.E.244.244;

35 Prodrugs of 5.G

5.G.228.228; 5.G.228.229; 5.G.228.230; 5.G.228.231; 5.G.228.236; 5.G.228.237;
 5.G.228.238; 5.G.228.239; 5.G.228.154; 5.G.228.157; 5.G.228.166; 5.G.228.169;
 5.G.228.172; 5.G.228.175; 5.G.228.240; 5.G.228.244; 5.G.229.228; 5.G.229.229;
 5.G.229.230; 5.G.229.231; 5.G.229.236; 5.G.229.237; 5.G.229.238; 5.G.229.239;
 40 5.G.229.154; 5.G.229.157; 5.G.229.166; 5.G.229.169; 5.G.229.172; 5.G.229.175;
 5.G.229.240; 5.G.229.244; 5.G.230.228; 5.G.230.229; 5.G.230.230; 5.G.230.231;
 5.G.230.236; 5.G.230.237; 5.G.230.238; 5.G.230.239; 5.G.230.154; 5.G.230.157;
 5.G.230.166; 5.G.230.169; 5.G.230.172; 5.G.230.175; 5.G.230.240; 5.G.230.244;
 5.G.231.228; 5.G.231.229; 5.G.231.230; 5.G.231.231; 5.G.231.236; 5.G.231.237;
 45 5.G.231.238; 5.G.231.239; 5.G.231.154; 5.G.231.157; 5.G.231.166; 5.G.231.169;
 5.G.231.172; 5.G.231.175; 5.G.231.240; 5.G.231.244; 5.G.236.228; 5.G.236.229;

- 5.G.236.230; 5.G.236.231; 5.G.236.236; 5.G.236.237; 5.G.236.238; 5.G.236.239;
 5.G.236.154; 5.G.236.157; 5.G.236.166; 5.G.236.169; 5.G.236.172; 5.G.236.175;
 5.G.236.240; 5.G.236.244; 5.G.237.228; 5.G.237.229; 5.G.237.230; 5.G.237.231;
 5.G.237.236; 5.G.237.237; 5.G.237.238; 5.G.237.239; 5.G.237.154; 5.G.237.157;
 5 5.G.237.166; 5.G.237.169; 5.G.237.172; 5.G.237.175; 5.G.237.240; 5.G.237.244;
 5.G.238.228; 5.G.238.229; 5.G.238.230; 5.G.238.231; 5.G.238.236; 5.G.238.237;
 5.G.238.238; 5.G.238.239; 5.G.238.154; 5.G.238.157; 5.G.238.166; 5.G.238.169;
 5.G.238.172; 5.G.238.175; 5.G.238.240; 5.G.238.244; 5.G.239.228; 5.G.239.229;
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 10 5.G.239.154; 5.G.239.157; 5.G.239.166; 5.G.239.169; 5.G.239.172; 5.G.239.175;
 5.G.239.240; 5.G.239.244; 5.G.154.228; 5.G.154.229; 5.G.154.230; 5.G.154.231;
 5.G.154.236; 5.G.154.237; 5.G.154.238; 5.G.154.239; 5.G.154.154; 5.G.154.157;
 5.G.154.166; 5.G.154.169; 5.G.154.172; 5.G.154.175; 5.G.154.240; 5.G.154.244;
 5.G.157.228; 5.G.157.229; 5.G.157.230; 5.G.157.231; 5.G.157.236; 5.G.157.237;
 15 5.G.157.238; 5.G.157.239; 5.G.157.154; 5.G.157.157; 5.G.157.166; 5.G.157.169;
 5.G.157.172; 5.G.157.175; 5.G.157.240; 5.G.157.244; 5.G.166.228; 5.G.166.229;
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 5.G.166.240; 5.G.166.244; 5.G.169.228; 5.G.169.229; 5.G.169.230; 5.G.169.231;
 20 5.G.169.236; 5.G.169.237; 5.G.169.238; 5.G.169.239; 5.G.169.154; 5.G.169.157;
 5.G.169.166; 5.G.169.169; 5.G.169.172; 5.G.169.175; 5.G.169.240; 5.G.169.244;
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 5.G.172.172; 5.G.172.175; 5.G.172.240; 5.G.172.244; 5.G.175.228; 5.G.175.229;
 25 5.G.175.230; 5.G.175.231; 5.G.175.236; 5.G.175.237; 5.G.175.238; 5.G.175.239;
 5.G.175.154; 5.G.175.157; 5.G.175.166; 5.G.175.169; 5.G.175.172; 5.G.175.175;
 5.G.175.240; 5.G.175.244; 5.G.240.228; 5.G.240.229; 5.G.240.230; 5.G.240.231;
 5.G.240.236; 5.G.240.237; 5.G.240.238; 5.G.240.239; 5.G.240.154; 5.G.240.157;
 5.G.240.166; 5.G.240.169; 5.G.240.172; 5.G.240.175; 5.G.240.240; 5.G.240.244;
 30 5.G.244.228; 5.G.244.229; 5.G.244.230; 5.G.244.231; 5.G.244.236; 5.G.244.237;
 5.G.244.238; 5.G.244.239; 5.G.244.154; 5.G.244.157; 5.G.244.166; 5.G.244.169;
 5.G.244.172; 5.G.244.175; 5.G.244.240; 5.G.244.244;

Prodrugs of 5.I

- 35 5.I.228.228; 5.I.228.229; 5.I.228.230; 5.I.228.231; 5.I.228.236; 5.I.228.237; 5.I.228.238;
 5.I.228.239; 5.I.228.154; 5.I.228.157; 5.I.228.166; 5.I.228.169; 5.I.228.172; 5.I.228.175;
 5.I.228.240; 5.I.228.244; 5.I.229.228; 5.I.229.229; 5.I.229.230; 5.I.229.231; 5.I.229.236;
 5.I.229.237; 5.I.229.238; 5.I.229.239; 5.I.229.154; 5.I.229.157; 5.I.229.166; 5.I.229.169;
 5.I.229.172; 5.I.229.175; 5.I.229.240; 5.I.229.244; 5.I.230.228; 5.I.230.229; 5.I.230.230;
 40 5.I.230.231; 5.I.230.236; 5.I.230.237; 5.I.230.238; 5.I.230.239; 5.I.230.154; 5.I.230.157;
 5.I.230.166; 5.I.230.169; 5.I.230.172; 5.I.230.175; 5.I.230.240; 5.I.230.244; 5.I.231.228;
 5.I.231.229; 5.I.231.230; 5.I.231.231; 5.I.231.236; 5.I.231.237; 5.I.231.238; 5.I.231.239;
 5.I.231.154; 5.I.231.157; 5.I.231.166; 5.I.231.169; 5.I.231.172; 5.I.231.175; 5.I.231.240;
 5.I.231.244; 5.I.236.228; 5.I.236.229; 5.I.236.230; 5.I.236.231; 5.I.236.236; 5.I.236.237;
 45 5.I.236.238; 5.I.236.239; 5.I.236.154; 5.I.236.157; 5.I.236.166; 5.I.236.169; 5.I.236.172;
 5.I.236.175; 5.I.236.240; 5.I.236.244; 5.I.237.228; 5.I.237.229; 5.I.237.230; 5.I.237.231;

5.I.237.236; 5.I.237.237; 5.I.237.238; 5.I.237.239; 5.I.237.154; 5.I.237.157; 5.I.237.166;
 5.I.237.169; 5.I.237.172; 5.I.237.175; 5.I.237.240; 5.I.237.244; 5.I.238.228; 5.I.238.229;
 5.I.238.230; 5.I.238.231; 5.I.238.236; 5.I.238.237; 5.I.238.238; 5.I.238.239; 5.I.238.154;
 5.I.238.157; 5.I.238.166; 5.I.238.169; 5.I.238.172; 5.I.238.175; 5.I.238.240; 5.I.238.244;
 5 5.I.239.228; 5.I.239.229; 5.I.239.230; 5.I.239.231; 5.I.239.236; 5.I.239.237; 5.I.239.238;
 5.I.239.239; 5.I.239.154; 5.I.239.157; 5.I.239.166; 5.I.239.169; 5.I.239.172; 5.I.239.175;
 5.I.239.240; 5.I.239.244; 5.I.154.228; 5.I.154.229; 5.I.154.230; 5.I.154.231; 5.I.154.236;
 5.I.154.237; 5.I.154.238; 5.I.154.239; 5.I.154.154; 5.I.154.157; 5.I.154.166; 5.I.154.169;
 5.I.154.172; 5.I.154.175; 5.I.154.240; 5.I.154.244; 5.I.157.228; 5.I.157.229; 5.I.157.230;
 10 5.I.157.231; 5.I.157.236; 5.I.157.237; 5.I.157.238; 5.I.157.239; 5.I.157.154; 5.I.157.157;
 5.I.157.166; 5.I.157.169; 5.I.157.172; 5.I.157.175; 5.I.157.240; 5.I.157.244; 5.I.166.228;
 5.I.166.229; 5.I.166.230; 5.I.166.231; 5.I.166.236; 5.I.166.237; 5.I.166.238; 5.I.166.239;
 5.I.166.154; 5.I.166.157; 5.I.166.166; 5.I.166.169; 5.I.166.172; 5.I.166.175; 5.I.166.240;
 5.I.166.244; 5.I.169.228; 5.I.169.229; 5.I.169.230; 5.I.169.231; 5.I.169.236; 5.I.169.237;
 15 5.I.169.238; 5.I.169.239; 5.I.169.154; 5.I.169.157; 5.I.169.166; 5.I.169.169; 5.I.169.172;
 5.I.169.175; 5.I.169.240; 5.I.169.244; 5.I.172.228; 5.I.172.229; 5.I.172.230; 5.I.172.231;
 5.I.172.236; 5.I.172.237; 5.I.172.238; 5.I.172.239; 5.I.172.154; 5.I.172.157; 5.I.172.166;
 5.I.172.169; 5.I.172.172; 5.I.172.175; 5.I.172.240; 5.I.172.244; 5.I.175.228; 5.I.175.229;
 5.I.175.230; 5.I.175.231; 5.I.175.236; 5.I.175.237; 5.I.175.238; 5.I.175.239; 5.I.175.154;
 20 5.I.175.157; 5.I.175.166; 5.I.175.169; 5.I.175.172; 5.I.175.175; 5.I.175.240; 5.I.175.244;
 5.I.240.228; 5.I.240.229; 5.I.240.230; 5.I.240.231; 5.I.240.236; 5.I.240.237; 5.I.240.238;
 5.I.240.239; 5.I.240.154; 5.I.240.157; 5.I.240.166; 5.I.240.169; 5.I.240.172; 5.I.240.175;
 5.I.240.240; 5.I.240.244; 5.I.244.228; 5.I.244.229; 5.I.244.230; 5.I.244.231; 5.I.244.236;
 5.I.244.237; 5.I.244.238; 5.I.244.239; 5.I.244.154; 5.I.244.157; 5.I.244.166; 5.I.244.169;
 25 5.I.244.172; 5.I.244.175; 5.I.244.240; 5.I.244.244;

Prodrugs of 5.J

5.J.228.228; 5.J.228.229; 5.J.228.230; 5.J.228.231; 5.J.228.236; 5.J.228.237; 5.J.228.238;
 5.J.228.239; 5.J.228.154; 5.J.228.157; 5.J.228.166; 5.J.228.169; 5.J.228.172; 5.J.228.175;
 30 5.J.228.240; 5.J.228.244; 5.J.229.228; 5.J.229.229; 5.J.229.230; 5.J.229.231; 5.J.229.236;
 5.J.229.237; 5.J.229.238; 5.J.229.239; 5.J.229.154; 5.J.229.157; 5.J.229.166; 5.J.229.169;
 5.J.229.172; 5.J.229.175; 5.J.229.240; 5.J.229.244; 5.J.230.228; 5.J.230.229; 5.J.230.230;
 5.J.230.231; 5.J.230.236; 5.J.230.237; 5.J.230.238; 5.J.230.239; 5.J.230.154; 5.J.230.157;
 5.J.230.166; 5.J.230.169; 5.J.230.172; 5.J.230.175; 5.J.230.240; 5.J.230.244; 5.J.231.228;
 35 5.J.231.229; 5.J.231.230; 5.J.231.231; 5.J.231.236; 5.J.231.237; 5.J.231.238; 5.J.231.239;
 5.J.231.154; 5.J.231.157; 5.J.231.166; 5.J.231.169; 5.J.231.172; 5.J.231.175; 5.J.231.240;
 5.J.231.244; 5.J.236.228; 5.J.236.229; 5.J.236.230; 5.J.236.231; 5.J.236.236; 5.J.236.237;
 5.J.236.238; 5.J.236.239; 5.J.236.154; 5.J.236.157; 5.J.236.166; 5.J.236.169; 5.J.236.172;
 5.J.236.175; 5.J.236.240; 5.J.236.244; 5.J.237.228; 5.J.237.229; 5.J.237.230; 5.J.237.231;
 40 5.J.237.236; 5.J.237.237; 5.J.237.238; 5.J.237.239; 5.J.237.154; 5.J.237.157; 5.J.237.166;
 5.J.237.169; 5.J.237.172; 5.J.237.175; 5.J.237.240; 5.J.237.244; 5.J.238.228; 5.J.238.229;
 5.J.238.230; 5.J.238.231; 5.J.238.236; 5.J.238.237; 5.J.238.238; 5.J.238.239; 5.J.238.154;
 5.J.238.157; 5.J.238.166; 5.J.238.169; 5.J.238.172; 5.J.238.175; 5.J.238.240; 5.J.238.244;
 5.J.239.228; 5.J.239.229; 5.J.239.230; 5.J.239.231; 5.J.239.236; 5.J.239.237; 5.J.239.238;
 45 5.J.239.239; 5.J.239.154; 5.J.239.157; 5.J.239.166; 5.J.239.169; 5.J.239.172; 5.J.239.175;
 5.J.239.240; 5.J.239.244; 5.J.154.228; 5.J.154.229; 5.J.154.230; 5.J.154.231; 5.J.154.236;

- 5.J.154.237; 5.J.154.238; 5.J.154.239; 5.J.154.154; 5.J.154.157; 5.J.154.166; 5.J.154.169;
 5.J.154.172; 5.J.154.175; 5.J.154.240; 5.J.154.244; 5.J.157.228; 5.J.157.229; 5.J.157.230;
 5.J.157.231; 5.J.157.236; 5.J.157.237; 5.J.157.238; 5.J.157.239; 5.J.157.154; 5.J.157.157;
 5.J.157.166; 5.J.157.169; 5.J.157.172; 5.J.157.175; 5.J.157.240; 5.J.157.244; 5.J.166.228;
 5 5.J.166.229; 5.J.166.230; 5.J.166.231; 5.J.166.236; 5.J.166.237; 5.J.166.238; 5.J.166.239;
 5.J.166.154; 5.J.166.157; 5.J.166.166; 5.J.166.169; 5.J.166.172; 5.J.166.175; 5.J.166.240;
 5.J.166.244; 5.J.169.228; 5.J.169.229; 5.J.169.230; 5.J.169.231; 5.J.169.236; 5.J.169.237;
 5.J.169.238; 5.J.169.239; 5.J.169.154; 5.J.169.157; 5.J.169.166; 5.J.169.169; 5.J.169.172;
 5.J.169.175; 5.J.169.240; 5.J.169.244; 5.J.172.228; 5.J.172.229; 5.J.172.230; 5.J.172.231;
 10 5.J.172.236; 5.J.172.237; 5.J.172.238; 5.J.172.239; 5.J.172.154; 5.J.172.157; 5.J.172.166;
 5.J.172.169; 5.J.172.172; 5.J.172.175; 5.J.172.240; 5.J.172.244; 5.J.175.228; 5.J.175.229;
 5.J.175.230; 5.J.175.231; 5.J.175.236; 5.J.175.237; 5.J.175.238; 5.J.175.239; 5.J.175.154;
 5.J.175.157; 5.J.175.166; 5.J.175.169; 5.J.175.172; 5.J.175.175; 5.J.175.240; 5.J.175.244;
 5.J.240.228; 5.J.240.229; 5.J.240.230; 5.J.240.231; 5.J.240.236; 5.J.240.237; 5.J.240.238;
 15 5.J.240.239; 5.J.240.154; 5.J.240.157; 5.J.240.166; 5.J.240.169; 5.J.240.172; 5.J.240.175;
 5.J.240.240; 5.J.240.244; 5.J.244.228; 5.J.244.229; 5.J.244.230; 5.J.244.231; 5.J.244.236;
 5.J.244.237; 5.J.244.238; 5.J.244.239; 5.J.244.154; 5.J.244.157; 5.J.244.166; 5.J.244.169;
 5.J.244.172; 5.J.244.175; 5.J.244.240; 5.J.244.244;
- 20 Prodrugs of 5.L
 5.L.228.228; 5.L.228.229; 5.L.228.230; 5.L.228.231; 5.L.228.236; 5.L.228.237;
 5.L.228.238; 5.L.228.239; 5.L.228.154; 5.L.228.157; 5.L.228.166; 5.L.228.169; 5.L.228.172;
 5.L.228.175; 5.L.228.240; 5.L.228.244; 5.L.229.228; 5.L.229.229; 5.L.229.230; 5.L.229.231;
 5.L.229.236; 5.L.229.237; 5.L.229.238; 5.L.229.239; 5.L.229.154; 5.L.229.157; 5.L.229.166;
 25 5.L.229.169; 5.L.229.172; 5.L.229.175; 5.L.229.240; 5.L.229.244; 5.L.230.228; 5.L.230.229;
 5.L.230.230; 5.L.230.231; 5.L.230.236; 5.L.230.237; 5.L.230.238; 5.L.230.239; 5.L.230.154;
 5.L.230.157; 5.L.230.166; 5.L.230.169; 5.L.230.172; 5.L.230.175; 5.L.230.240; 5.L.230.244;
 5.L.231.228; 5.L.231.229; 5.L.231.230; 5.L.231.231; 5.L.231.236; 5.L.231.237; 5.L.231.238;
 5.L.231.239; 5.L.231.154; 5.L.231.157; 5.L.231.166; 5.L.231.169; 5.L.231.172; 5.L.231.175;
 30 5.L.231.240; 5.L.231.244; 5.L.236.228; 5.L.236.229; 5.L.236.230; 5.L.236.231; 5.L.236.236;
 5.L.236.237; 5.L.236.238; 5.L.236.239; 5.L.236.154; 5.L.236.157; 5.L.236.166; 5.L.236.169;
 5.L.236.172; 5.L.236.175; 5.L.236.240; 5.L.236.244; 5.L.237.228; 5.L.237.229; 5.L.237.230;
 5.L.237.231; 5.L.237.236; 5.L.237.237; 5.L.237.238; 5.L.237.239; 5.L.237.154; 5.L.237.157;
 5.L.237.166; 5.L.237.169; 5.L.237.172; 5.L.237.175; 5.L.237.240; 5.L.237.244; 5.L.238.228;
 35 5.L.238.229; 5.L.238.230; 5.L.238.231; 5.L.238.236; 5.L.238.237; 5.L.238.238; 5.L.238.239;
 5.L.238.154; 5.L.238.157; 5.L.238.166; 5.L.238.169; 5.L.238.172; 5.L.238.175; 5.L.238.240;
 5.L.238.244; 5.L.239.228; 5.L.239.229; 5.L.239.230; 5.L.239.231; 5.L.239.236; 5.L.239.237;
 5.L.239.238; 5.L.239.239; 5.L.239.154; 5.L.239.157; 5.L.239.166; 5.L.239.169; 5.L.239.172;
 5.L.239.175; 5.L.239.240; 5.L.239.244; 5.L.154.228; 5.L.154.229; 5.L.154.230; 5.L.154.231;
 40 5.L.154.236; 5.L.154.237; 5.L.154.238; 5.L.154.239; 5.L.154.154; 5.L.154.157; 5.L.154.166;
 5.L.154.169; 5.L.154.172; 5.L.154.175; 5.L.154.240; 5.L.154.244; 5.L.157.228; 5.L.157.229;
 5.L.157.230; 5.L.157.231; 5.L.157.236; 5.L.157.237; 5.L.157.238; 5.L.157.239; 5.L.157.154;
 5.L.157.157; 5.L.157.166; 5.L.157.169; 5.L.157.172; 5.L.157.175; 5.L.157.240; 5.L.157.244;
 5.L.166.228; 5.L.166.229; 5.L.166.230; 5.L.166.231; 5.L.166.236; 5.L.166.237; 5.L.166.238;
 45 5.L.166.239; 5.L.166.154; 5.L.166.157; 5.L.166.166; 5.L.166.169; 5.L.166.172; 5.L.166.175;
 5.L.166.240; 5.L.166.244; 5.L.169.228; 5.L.169.229; 5.L.169.230; 5.L.169.231; 5.L.169.236;

5.L.169.237; 5.L.169.238; 5.L.169.239; 5.L.169.154; 5.L.169.157; 5.L.169.166; 5.L.169.169;
 5.L.169.172; 5.L.169.175; 5.L.169.240; 5.L.169.244; 5.L.172.228; 5.L.172.229; 5.L.172.230;
 5.L.172.231; 5.L.172.236; 5.L.172.237; 5.L.172.238; 5.L.172.239; 5.L.172.154; 5.L.172.157;
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 5 5.L.175.229; 5.L.175.230; 5.L.175.231; 5.L.175.236; 5.L.175.237; 5.L.175.238; 5.L.175.239;
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 5.L.240.238; 5.L.240.239; 5.L.240.154; 5.L.240.157; 5.L.240.166; 5.L.240.169; 5.L.240.172;
 5.L.240.175; 5.L.240.240; 5.L.240.244; 5.L.244.228; 5.L.244.229; 5.L.244.230; 5.L.244.231;
 10 5.L.244.236; 5.L.244.237; 5.L.244.238; 5.L.244.239; 5.L.244.154; 5.L.244.157; 5.L.244.166;
 5.L.244.169; 5.L.244.172; 5.L.244.175; 5.L.244.240; 5.L.244.244;

Prodrugs of 5.O

5.O.228.228; 5.O.228.229; 5.O.228.230; 5.O.228.231; 5.O.228.236; 5.O.228.237;
 15 5.O.228.238; 5.O.228.239; 5.O.228.154; 5.O.228.157; 5.O.228.166; 5.O.228.169;
 5.O.228.172; 5.O.228.175; 5.O.228.240; 5.O.228.244; 5.O.229.228; 5.O.229.229;
 5.O.229.230; 5.O.229.231; 5.O.229.236; 5.O.229.237; 5.O.229.238; 5.O.229.239;
 5.O.229.154; 5.O.229.157; 5.O.229.166; 5.O.229.169; 5.O.229.172; 5.O.229.175;
 5.O.229.240; 5.O.229.244; 5.O.230.228; 5.O.230.229; 5.O.230.230; 5.O.230.231;
 20 5.O.230.236; 5.O.230.237; 5.O.230.238; 5.O.230.239; 5.O.230.154; 5.O.230.157;
 5.O.230.166; 5.O.230.169; 5.O.230.172; 5.O.230.175; 5.O.230.240; 5.O.230.244;
 5.O.231.228; 5.O.231.229; 5.O.231.230; 5.O.231.231; 5.O.231.236; 5.O.231.237;
 5.O.231.238; 5.O.231.239; 5.O.231.154; 5.O.231.157; 5.O.231.166; 5.O.231.169;
 5.O.231.172; 5.O.231.175; 5.O.231.240; 5.O.231.244; 5.O.236.228; 5.O.236.229;
 25 5.O.236.230; 5.O.236.231; 5.O.236.236; 5.O.236.237; 5.O.236.238; 5.O.236.239;
 5.O.236.154; 5.O.236.157; 5.O.236.166; 5.O.236.169; 5.O.236.172; 5.O.236.175;
 5.O.236.240; 5.O.236.244; 5.O.237.228; 5.O.237.229; 5.O.237.230; 5.O.237.231;
 5.O.237.236; 5.O.237.237; 5.O.237.238; 5.O.237.239; 5.O.237.154; 5.O.237.157;
 5.O.237.166; 5.O.237.169; 5.O.237.172; 5.O.237.175; 5.O.237.240; 5.O.237.244;
 30 5.O.238.228; 5.O.238.229; 5.O.238.230; 5.O.238.231; 5.O.238.236; 5.O.238.237;
 5.O.238.238; 5.O.238.239; 5.O.238.154; 5.O.238.157; 5.O.238.166; 5.O.238.169;
 5.O.238.172; 5.O.238.175; 5.O.238.240; 5.O.238.244; 5.O.239.228; 5.O.239.229;
 5.O.239.230; 5.O.239.231; 5.O.239.236; 5.O.239.237; 5.O.239.238; 5.O.239.239;
 5.O.239.154; 5.O.239.157; 5.O.239.166; 5.O.239.169; 5.O.239.172; 5.O.239.175;
 35 5.O.239.240; 5.O.239.244; 5.O.154.228; 5.O.154.229; 5.O.154.230; 5.O.154.231;
 5.O.154.236; 5.O.154.237; 5.O.154.238; 5.O.154.239; 5.O.154.154; 5.O.154.157;
 5.O.154.166; 5.O.154.169; 5.O.154.172; 5.O.154.175; 5.O.154.240; 5.O.154.244;
 5.O.157.228; 5.O.157.229; 5.O.157.230; 5.O.157.231; 5.O.157.236; 5.O.157.237;
 5.O.157.238; 5.O.157.239; 5.O.157.154; 5.O.157.157; 5.O.157.166; 5.O.157.169;
 40 5.O.157.172; 5.O.157.175; 5.O.157.240; 5.O.157.244; 5.O.166.228; 5.O.166.229;
 5.O.166.230; 5.O.166.231; 5.O.166.236; 5.O.166.237; 5.O.166.238; 5.O.166.239;
 5.O.166.154; 5.O.166.157; 5.O.166.166; 5.O.166.169; 5.O.166.172; 5.O.166.175;
 5.O.166.240; 5.O.166.244; 5.O.169.228; 5.O.169.229; 5.O.169.230; 5.O.169.231;
 5.O.169.236; 5.O.169.237; 5.O.169.238; 5.O.169.239; 5.O.169.154; 5.O.169.157;
 45 5.O.169.166; 5.O.169.169; 5.O.169.172; 5.O.169.175; 5.O.169.240; 5.O.169.244;
 5.O.172.228; 5.O.172.229; 5.O.172.230; 5.O.172.231; 5.O.172.236; 5.O.172.237;

5.O.172.238; 5.O.172.239; 5.O.172.154; 5.O.172.157; 5.O.172.166; 5.O.172.169;
 5.O.172.172; 5.O.172.175; 5.O.172.240; 5.O.172.244; 5.O.175.228; 5.O.175.229;
 5.O.175.230; 5.O.175.231; 5.O.175.236; 5.O.175.237; 5.O.175.238; 5.O.175.239;
 5.O.175.154; 5.O.175.157; 5.O.175.166; 5.O.175.169; 5.O.175.172; 5.O.175.175;
 5 5.O.175.240; 5.O.175.244; 5.O.240.228; 5.O.240.229; 5.O.240.230; 5.O.240.231;
 5.O.240.236; 5.O.240.237; 5.O.240.238; 5.O.240.239; 5.O.240.154; 5.O.240.157;
 5.O.240.166; 5.O.240.169; 5.O.240.172; 5.O.240.175; 5.O.240.240; 5.O.240.244;
 5.O.244.228; 5.O.244.229; 5.O.244.230; 5.O.244.231; 5.O.244.236; 5.O.244.237;
 5.O.244.238; 5.O.244.239; 5.O.244.154; 5.O.244.157; 5.O.244.166; 5.O.244.169;
 10 5.O.244.172; 5.O.244.175; 5.O.244.240; 5.O.244.244;

Prodrugs of 5.P

5.P.228.228; 5.P.228.229; 5.P.228.230; 5.P.228.231; 5.P.228.236; 5.P.228.237;
 5.P.228.238; 5.P.228.239; 5.P.228.154; 5.P.228.157; 5.P.228.166; 5.P.228.169; 5.P.228.172;
 15 5.P.228.175; 5.P.228.240; 5.P.228.244; 5.P.229.228; 5.P.229.229; 5.P.229.230; 5.P.229.231;
 5.P.229.236; 5.P.229.237; 5.P.229.238; 5.P.229.239; 5.P.229.154; 5.P.229.157; 5.P.229.166;
 5.P.229.169; 5.P.229.172; 5.P.229.175; 5.P.229.240; 5.P.229.244; 5.P.230.228; 5.P.230.229;
 5.P.230.230; 5.P.230.231; 5.P.230.236; 5.P.230.237; 5.P.230.238; 5.P.230.239; 5.P.230.154;
 5.P.230.157; 5.P.230.166; 5.P.230.169; 5.P.230.172; 5.P.230.175; 5.P.230.240; 5.P.230.244;
 20 5.P.231.228; 5.P.231.229; 5.P.231.230; 5.P.231.231; 5.P.231.236; 5.P.231.237; 5.P.231.238;
 5.P.231.239; 5.P.231.154; 5.P.231.157; 5.P.231.166; 5.P.231.169; 5.P.231.172; 5.P.231.175;
 5.P.231.240; 5.P.231.244; 5.P.236.228; 5.P.236.229; 5.P.236.230; 5.P.236.231; 5.P.236.236;
 5.P.236.237; 5.P.236.238; 5.P.236.239; 5.P.236.154; 5.P.236.157; 5.P.236.166; 5.P.236.169;
 5.P.236.172; 5.P.236.175; 5.P.236.240; 5.P.236.244; 5.P.237.228; 5.P.237.229; 5.P.237.230;
 25 5.P.237.231; 5.P.237.236; 5.P.237.237; 5.P.237.238; 5.P.237.239; 5.P.237.154; 5.P.237.157;
 5.P.237.166; 5.P.237.169; 5.P.237.172; 5.P.237.175; 5.P.237.240; 5.P.237.244; 5.P.238.228;
 5.P.238.229; 5.P.238.230; 5.P.238.231; 5.P.238.236; 5.P.238.237; 5.P.238.238; 5.P.238.239;
 5.P.238.154; 5.P.238.157; 5.P.238.166; 5.P.238.169; 5.P.238.172; 5.P.238.175; 5.P.238.240;
 5.P.238.244; 5.P.239.228; 5.P.239.229; 5.P.239.230; 5.P.239.231; 5.P.239.236; 5.P.239.237;
 30 5.P.239.238; 5.P.239.239; 5.P.239.154; 5.P.239.157; 5.P.239.166; 5.P.239.169; 5.P.239.172;
 5.P.239.175; 5.P.239.240; 5.P.239.244; 5.P.154.228; 5.P.154.229; 5.P.154.230; 5.P.154.231;
 5.P.154.236; 5.P.154.237; 5.P.154.238; 5.P.154.239; 5.P.154.154; 5.P.154.157; 5.P.154.166;
 5.P.154.169; 5.P.154.172; 5.P.154.175; 5.P.154.240; 5.P.154.244; 5.P.157.228; 5.P.157.229;
 5.P.157.230; 5.P.157.231; 5.P.157.236; 5.P.157.237; 5.P.157.238; 5.P.157.239; 5.P.157.154;
 35 5.P.157.157; 5.P.157.166; 5.P.157.169; 5.P.157.172; 5.P.157.175; 5.P.157.240; 5.P.157.244;
 5.P.166.228; 5.P.166.229; 5.P.166.230; 5.P.166.231; 5.P.166.236; 5.P.166.237; 5.P.166.238;
 5.P.166.239; 5.P.166.154; 5.P.166.157; 5.P.166.166; 5.P.166.169; 5.P.166.172; 5.P.166.175;
 5.P.166.240; 5.P.166.244; 5.P.169.228; 5.P.169.229; 5.P.169.230; 5.P.169.231; 5.P.169.236;
 5.P.169.237; 5.P.169.238; 5.P.169.239; 5.P.169.154; 5.P.169.157; 5.P.169.166; 5.P.169.169;
 40 5.P.169.172; 5.P.169.175; 5.P.169.240; 5.P.169.244; 5.P.172.228; 5.P.172.229; 5.P.172.230;
 5.P.172.231; 5.P.172.236; 5.P.172.237; 5.P.172.238; 5.P.172.239; 5.P.172.154; 5.P.172.157;
 5.P.172.166; 5.P.172.169; 5.P.172.172; 5.P.172.175; 5.P.172.240; 5.P.172.244; 5.P.175.228;
 5.P.175.229; 5.P.175.230; 5.P.175.231; 5.P.175.236; 5.P.175.237; 5.P.175.238; 5.P.175.239;
 5.P.175.154; 5.P.175.157; 5.P.175.166; 5.P.175.169; 5.P.175.172; 5.P.175.175; 5.P.175.240;
 45 5.P.175.244; 5.P.240.228; 5.P.240.229; 5.P.240.230; 5.P.240.231; 5.P.240.236; 5.P.240.237;
 5.P.240.238; 5.P.240.239; 5.P.240.154; 5.P.240.157; 5.P.240.166; 5.P.240.169; 5.P.240.172;

5.P.240.175; 5.P.240.240; 5.P.240.244; 5.P.244.228; 5.P.244.229; 5.P.244.230; 5.P.244.231;
 5.P.244.236; 5.P.244.237; 5.P.244.238; 5.P.244.239; 5.P.244.154; 5.P.244.157; 5.P.244.166;
 5.P.244.169; 5.P.244.172; 5.P.244.175; 5.P.244.240; 5.P.244.244;

5 Prodrugs of 5.U

5.U.228.228; 5.U.228.229; 5.U.228.230; 5.U.228.231; 5.U.228.236; 5.U.228.237;
 5.U.228.238; 5.U.228.239; 5.U.228.154; 5.U.228.157; 5.U.228.166; 5.U.228.169;
 5.U.228.172; 5.U.228.175; 5.U.228.240; 5.U.228.244; 5.U.229.228; 5.U.229.229;
 5.U.229.230; 5.U.229.231; 5.U.229.236; 5.U.229.237; 5.U.229.238; 5.U.229.239;
 10 5.U.229.154; 5.U.229.157; 5.U.229.166; 5.U.229.169; 5.U.229.172; 5.U.229.175;
 5.U.229.240; 5.U.229.244; 5.U.230.228; 5.U.230.229; 5.U.230.230; 5.U.230.231;
 5.U.230.236; 5.U.230.237; 5.U.230.238; 5.U.230.239; 5.U.230.154; 5.U.230.157;
 5.U.230.166; 5.U.230.169; 5.U.230.172; 5.U.230.175; 5.U.230.240; 5.U.230.244;
 5.U.231.228; 5.U.231.229; 5.U.231.230; 5.U.231.231; 5.U.231.236; 5.U.231.237;
 15 5.U.231.238; 5.U.231.239; 5.U.231.154; 5.U.231.157; 5.U.231.166; 5.U.231.169;
 5.U.231.172; 5.U.231.175; 5.U.231.240; 5.U.231.244; 5.U.236.228; 5.U.236.229;
 5.U.236.230; 5.U.236.231; 5.U.236.236; 5.U.236.237; 5.U.236.238; 5.U.236.239;
 5.U.236.154; 5.U.236.157; 5.U.236.166; 5.U.236.169; 5.U.236.172; 5.U.236.175;
 5.U.236.240; 5.U.236.244; 5.U.237.228; 5.U.237.229; 5.U.237.230; 5.U.237.231;
 20 5.U.237.236; 5.U.237.237; 5.U.237.238; 5.U.237.239; 5.U.237.154; 5.U.237.157;
 5.U.237.166; 5.U.237.169; 5.U.237.172; 5.U.237.175; 5.U.237.240; 5.U.237.244;
 5.U.238.228; 5.U.238.229; 5.U.238.230; 5.U.238.231; 5.U.238.236; 5.U.238.237;
 5.U.238.238; 5.U.238.239; 5.U.238.154; 5.U.238.157; 5.U.238.166; 5.U.238.169;
 5.U.238.172; 5.U.238.175; 5.U.238.240; 5.U.238.244; 5.U.239.228; 5.U.239.229;
 25 5.U.239.230; 5.U.239.231; 5.U.239.236; 5.U.239.237; 5.U.239.238; 5.U.239.239;
 5.U.239.154; 5.U.239.157; 5.U.239.166; 5.U.239.169; 5.U.239.172; 5.U.239.175;
 5.U.239.240; 5.U.239.244; 5.U.154.228; 5.U.154.229; 5.U.154.230; 5.U.154.231;
 5.U.154.236; 5.U.154.237; 5.U.154.238; 5.U.154.239; 5.U.154.154; 5.U.154.157;
 5.U.154.166; 5.U.154.169; 5.U.154.172; 5.U.154.175; 5.U.154.240; 5.U.154.244;
 30 5.U.157.228; 5.U.157.229; 5.U.157.230; 5.U.157.231; 5.U.157.236; 5.U.157.237;
 5.U.157.238; 5.U.157.239; 5.U.157.154; 5.U.157.157; 5.U.157.166; 5.U.157.169;
 5.U.157.172; 5.U.157.175; 5.U.157.240; 5.U.157.244; 5.U.166.228; 5.U.166.229;
 5.U.166.230; 5.U.166.231; 5.U.166.236; 5.U.166.237; 5.U.166.238; 5.U.166.239;
 5.U.166.154; 5.U.166.157; 5.U.166.166; 5.U.166.169; 5.U.166.172; 5.U.166.175;
 35 5.U.166.240; 5.U.166.244; 5.U.169.228; 5.U.169.229; 5.U.169.230; 5.U.169.231;
 5.U.169.236; 5.U.169.237; 5.U.169.238; 5.U.169.239; 5.U.169.154; 5.U.169.157;
 5.U.169.166; 5.U.169.169; 5.U.169.172; 5.U.169.175; 5.U.169.240; 5.U.169.244;
 5.U.172.228; 5.U.172.229; 5.U.172.230; 5.U.172.231; 5.U.172.236; 5.U.172.237;
 5.U.172.238; 5.U.172.239; 5.U.172.154; 5.U.172.157; 5.U.172.166; 5.U.172.169;
 40 5.U.172.172; 5.U.172.175; 5.U.172.240; 5.U.172.244; 5.U.175.228; 5.U.175.229;
 5.U.175.230; 5.U.175.231; 5.U.175.236; 5.U.175.237; 5.U.175.238; 5.U.175.239;
 5.U.175.154; 5.U.175.157; 5.U.175.166; 5.U.175.169; 5.U.175.172; 5.U.175.175;
 5.U.175.240; 5.U.175.244; 5.U.240.228; 5.U.240.229; 5.U.240.230; 5.U.240.231;
 5.U.240.236; 5.U.240.237; 5.U.240.238; 5.U.240.239; 5.U.240.154; 5.U.240.157;
 45 5.U.240.166; 5.U.240.169; 5.U.240.172; 5.U.240.175; 5.U.240.240; 5.U.240.244;
 5.U.244.228; 5.U.244.229; 5.U.244.230; 5.U.244.231; 5.U.244.236; 5.U.244.237;

5.U.244.238; 5.U.244.239; 5.U.244.154; 5.U.244.157; 5.U.244.166; 5.U.244.169;
5.U.244.172; 5.U.244.175; 5.U.244.240; 5.U.244.244;

Prodrugs of 5.W

5 5.W.228.228; 5.W.228.229; 5.W.228.230; 5.W.228.231; 5.W.228.236; 5.W.228.237;
5.W.228.238; 5.W.228.239; 5.W.228.154; 5.W.228.157; 5.W.228.166; 5.W.228.169;
5.W.228.172; 5.W.228.175; 5.W.228.240; 5.W.228.244; 5.W.229.228; 5.W.229.229;
5.W.229.230; 5.W.229.231; 5.W.229.236; 5.W.229.237; 5.W.229.238; 5.W.229.239;
5.W.229.154; 5.W.229.157; 5.W.229.166; 5.W.229.169; 5.W.229.172; 5.W.229.175;
10 5.W.229.240; 5.W.229.244; 5.W.230.228; 5.W.230.229; 5.W.230.230; 5.W.230.231;
5.W.230.236; 5.W.230.237; 5.W.230.238; 5.W.230.239; 5.W.230.154; 5.W.230.157;
5.W.230.166; 5.W.230.169; 5.W.230.172; 5.W.230.175; 5.W.230.240; 5.W.230.244;
5.W.231.228; 5.W.231.229; 5.W.231.230; 5.W.231.231; 5.W.231.236; 5.W.231.237;
5.W.231.238; 5.W.231.239; 5.W.231.154; 5.W.231.157; 5.W.231.166; 5.W.231.169;
15 5.W.231.172; 5.W.231.175; 5.W.231.240; 5.W.231.244; 5.W.236.228; 5.W.236.229;
5.W.236.230; 5.W.236.231; 5.W.236.236; 5.W.236.237; 5.W.236.238; 5.W.236.239;
5.W.236.154; 5.W.236.157; 5.W.236.166; 5.W.236.169; 5.W.236.172; 5.W.236.175;
5.W.236.240; 5.W.236.244; 5.W.237.228; 5.W.237.229; 5.W.237.230; 5.W.237.231;
5.W.237.236; 5.W.237.237; 5.W.237.238; 5.W.237.239; 5.W.237.154; 5.W.237.157;
20 5.W.237.166; 5.W.237.169; 5.W.237.172; 5.W.237.175; 5.W.237.240; 5.W.237.244;
5.W.238.228; 5.W.238.229; 5.W.238.230; 5.W.238.231; 5.W.238.236; 5.W.238.237;
5.W.238.238; 5.W.238.239; 5.W.238.154; 5.W.238.157; 5.W.238.166; 5.W.238.169;
5.W.238.172; 5.W.238.175; 5.W.238.240; 5.W.238.244; 5.W.239.228; 5.W.239.229;
5.W.239.230; 5.W.239.231; 5.W.239.236; 5.W.239.237; 5.W.239.238; 5.W.239.239;
25 5.W.239.154; 5.W.239.157; 5.W.239.166; 5.W.239.169; 5.W.239.172; 5.W.239.175;
5.W.239.240; 5.W.239.244; 5.W.154.228; 5.W.154.229; 5.W.154.230; 5.W.154.231;
5.W.154.236; 5.W.154.237; 5.W.154.238; 5.W.154.239; 5.W.154.154; 5.W.154.157;
5.W.154.166; 5.W.154.169; 5.W.154.172; 5.W.154.175; 5.W.154.240; 5.W.154.244;
5.W.157.228; 5.W.157.229; 5.W.157.230; 5.W.157.231; 5.W.157.236; 5.W.157.237;
30 5.W.157.238; 5.W.157.239; 5.W.157.154; 5.W.157.157; 5.W.157.166; 5.W.157.169;
5.W.157.172; 5.W.157.175; 5.W.157.240; 5.W.157.244; 5.W.166.228; 5.W.166.229;
5.W.166.230; 5.W.166.231; 5.W.166.236; 5.W.166.237; 5.W.166.238; 5.W.166.239;
5.W.166.154; 5.W.166.157; 5.W.166.166; 5.W.166.169; 5.W.166.172; 5.W.166.175;
5.W.166.240; 5.W.166.244; 5.W.169.228; 5.W.169.229; 5.W.169.230; 5.W.169.231;
35 5.W.169.236; 5.W.169.237; 5.W.169.238; 5.W.169.239; 5.W.169.154; 5.W.169.157;
5.W.169.166; 5.W.169.169; 5.W.169.172; 5.W.169.175; 5.W.169.240; 5.W.169.244;
5.W.172.228; 5.W.172.229; 5.W.172.230; 5.W.172.231; 5.W.172.236; 5.W.172.237;
5.W.172.238; 5.W.172.239; 5.W.172.154; 5.W.172.157; 5.W.172.166; 5.W.172.169;
5.W.172.172; 5.W.172.175; 5.W.172.240; 5.W.172.244; 5.W.175.228; 5.W.175.229;
40 5.W.175.230; 5.W.175.231; 5.W.175.236; 5.W.175.237; 5.W.175.238; 5.W.175.239;
5.W.175.154; 5.W.175.157; 5.W.175.166; 5.W.175.169; 5.W.175.172; 5.W.175.175;
5.W.175.240; 5.W.175.244; 5.W.240.228; 5.W.240.229; 5.W.240.230; 5.W.240.231;
5.W.240.236; 5.W.240.237; 5.W.240.238; 5.W.240.239; 5.W.240.154; 5.W.240.157;
5.W.240.166; 5.W.240.169; 5.W.240.172; 5.W.240.175; 5.W.240.240; 5.W.240.244;
45 5.W.244.228; 5.W.244.229; 5.W.244.230; 5.W.244.231; 5.W.244.236; 5.W.244.237;

5.W.244.238; 5.W.244.239; 5.W.244.154; 5.W.244.157; 5.W.244.166; 5.W.244.169;
5.W.244.172; 5.W.244.175; 5.W.244.240; 5.W.244.244;

Prodrugs of 5.Y

- 5 5.Y.228.228; 5.Y.228.229; 5.Y.228.230; 5.Y.228.231; 5.Y.228.236; 5.Y.228.237;
5.Y.228.238; 5.Y.228.239; 5.Y.228.154; 5.Y.228.157; 5.Y.228.166; 5.Y.228.169;
5.Y.228.172; 5.Y.228.175; 5.Y.228.240; 5.Y.228.244; 5.Y.229.228; 5.Y.229.229;
5.Y.229.230; 5.Y.229.231; 5.Y.229.236; 5.Y.229.237; 5.Y.229.238; 5.Y.229.239;
5.Y.229.154; 5.Y.229.157; 5.Y.229.166; 5.Y.229.169; 5.Y.229.172; 5.Y.229.175;
10 5.Y.229.240; 5.Y.229.244; 5.Y.230.228; 5.Y.230.229; 5.Y.230.230; 5.Y.230.231;
5.Y.230.236; 5.Y.230.237; 5.Y.230.238; 5.Y.230.239; 5.Y.230.154; 5.Y.230.157;
5.Y.230.166; 5.Y.230.169; 5.Y.230.172; 5.Y.230.175; 5.Y.230.240; 5.Y.230.244;
5.Y.231.228; 5.Y.231.229; 5.Y.231.230; 5.Y.231.231; 5.Y.231.236; 5.Y.231.237;
5.Y.231.238; 5.Y.231.239; 5.Y.231.154; 5.Y.231.157; 5.Y.231.166; 5.Y.231.169;
15 5.Y.231.172; 5.Y.231.175; 5.Y.231.240; 5.Y.231.244; 5.Y.236.228; 5.Y.236.229;
5.Y.236.230; 5.Y.236.231; 5.Y.236.236; 5.Y.236.237; 5.Y.236.238; 5.Y.236.239;
5.Y.236.154; 5.Y.236.157; 5.Y.236.166; 5.Y.236.169; 5.Y.236.172; 5.Y.236.175;
5.Y.236.240; 5.Y.236.244; 5.Y.237.228; 5.Y.237.229; 5.Y.237.230; 5.Y.237.231;
5.Y.237.236; 5.Y.237.237; 5.Y.237.238; 5.Y.237.239; 5.Y.237.154; 5.Y.237.157;
20 5.Y.237.166; 5.Y.237.169; 5.Y.237.172; 5.Y.237.175; 5.Y.237.240; 5.Y.237.244;
5.Y.238.228; 5.Y.238.229; 5.Y.238.230; 5.Y.238.231; 5.Y.238.236; 5.Y.238.237;
5.Y.238.238; 5.Y.238.239; 5.Y.238.154; 5.Y.238.157; 5.Y.238.166; 5.Y.238.169;
5.Y.238.172; 5.Y.238.175; 5.Y.238.240; 5.Y.238.244; 5.Y.239.228; 5.Y.239.229;
5.Y.239.230; 5.Y.239.231; 5.Y.239.236; 5.Y.239.237; 5.Y.239.238; 5.Y.239.239;
25 5.Y.239.154; 5.Y.239.157; 5.Y.239.166; 5.Y.239.169; 5.Y.239.172; 5.Y.239.175;
5.Y.239.240; 5.Y.239.244; 5.Y.154.228; 5.Y.154.229; 5.Y.154.230; 5.Y.154.231;
5.Y.154.236; 5.Y.154.237; 5.Y.154.238; 5.Y.154.239; 5.Y.154.154; 5.Y.154.157;
5.Y.154.166; 5.Y.154.169; 5.Y.154.172; 5.Y.154.175; 5.Y.154.240; 5.Y.154.244;
5.Y.157.228; 5.Y.157.229; 5.Y.157.230; 5.Y.157.231; 5.Y.157.236; 5.Y.157.237;
30 5.Y.157.238; 5.Y.157.239; 5.Y.157.154; 5.Y.157.157; 5.Y.157.166; 5.Y.157.169;
5.Y.157.172; 5.Y.157.175; 5.Y.157.240; 5.Y.157.244; 5.Y.166.228; 5.Y.166.229;
5.Y.166.230; 5.Y.166.231; 5.Y.166.236; 5.Y.166.237; 5.Y.166.238; 5.Y.166.239;
5.Y.166.154; 5.Y.166.157; 5.Y.166.166; 5.Y.166.169; 5.Y.166.172; 5.Y.166.175;
5.Y.166.240; 5.Y.166.244; 5.Y.169.228; 5.Y.169.229; 5.Y.169.230; 5.Y.169.231;
35 5.Y.169.236; 5.Y.169.237; 5.Y.169.238; 5.Y.169.239; 5.Y.169.154; 5.Y.169.157;
5.Y.169.166; 5.Y.169.169; 5.Y.169.172; 5.Y.169.175; 5.Y.169.240; 5.Y.169.244;
5.Y.172.228; 5.Y.172.229; 5.Y.172.230; 5.Y.172.231; 5.Y.172.236; 5.Y.172.237;
5.Y.172.238; 5.Y.172.239; 5.Y.172.154; 5.Y.172.157; 5.Y.172.166; 5.Y.172.169;
5.Y.172.172; 5.Y.172.175; 5.Y.172.240; 5.Y.172.244; 5.Y.175.228; 5.Y.175.229;
40 5.Y.175.230; 5.Y.175.231; 5.Y.175.236; 5.Y.175.237; 5.Y.175.238; 5.Y.175.239;
5.Y.175.154; 5.Y.175.157; 5.Y.175.166; 5.Y.175.169; 5.Y.175.172; 5.Y.175.175;
5.Y.175.240; 5.Y.175.244; 5.Y.240.228; 5.Y.240.229; 5.Y.240.230; 5.Y.240.231;
5.Y.240.236; 5.Y.240.237; 5.Y.240.238; 5.Y.240.239; 5.Y.240.154; 5.Y.240.157;
5.Y.240.166; 5.Y.240.169; 5.Y.240.172; 5.Y.240.175; 5.Y.240.240; 5.Y.240.244;
45 5.Y.244.228; 5.Y.244.229; 5.Y.244.230; 5.Y.244.231; 5.Y.244.236; 5.Y.244.237;

5.Y.244.238; 5.Y.244.239; 5.Y.244.154; 5.Y.244.157; 5.Y.244.166; 5.Y.244.169;
5.Y.244.172; 5.Y.244.175; 5.Y.244.240; 5.Y.244.244;

Prodrugs of 6.B

- 5 6.B.228.228; 6.B.228.229; 6.B.228.230; 6.B.228.231; 6.B.228.236; 6.B.228.237;
6.B.228.238; 6.B.228.239; 6.B.228.154; 6.B.228.157; 6.B.228.166; 6.B.228.169; 6.B.228.172;
6.B.228.175; 6.B.228.240; 6.B.228.244; 6.B.229.228; 6.B.229.229; 6.B.229.230; 6.B.229.231;
6.B.229.236; 6.B.229.237; 6.B.229.238; 6.B.229.239; 6.B.229.154; 6.B.229.157; 6.B.229.166;
6.B.229.169; 6.B.229.172; 6.B.229.175; 6.B.229.240; 6.B.229.244; 6.B.230.228; 6.B.230.229;
10 6.B.230.230; 6.B.230.231; 6.B.230.236; 6.B.230.237; 6.B.230.238; 6.B.230.239; 6.B.230.154;
6.B.230.157; 6.B.230.166; 6.B.230.169; 6.B.230.172; 6.B.230.175; 6.B.230.240; 6.B.230.244;
6.B.231.228; 6.B.231.229; 6.B.231.230; 6.B.231.231; 6.B.231.236; 6.B.231.237; 6.B.231.238;
6.B.231.239; 6.B.231.154; 6.B.231.157; 6.B.231.166; 6.B.231.169; 6.B.231.172; 6.B.231.175;
6.B.231.240; 6.B.231.244; 6.B.236.228; 6.B.236.229; 6.B.236.230; 6.B.236.231; 6.B.236.236;
15 6.B.236.237; 6.B.236.238; 6.B.236.239; 6.B.236.154; 6.B.236.157; 6.B.236.166; 6.B.236.169;
6.B.236.172; 6.B.236.175; 6.B.236.240; 6.B.236.244; 6.B.237.228; 6.B.237.229; 6.B.237.230;
6.B.237.231; 6.B.237.236; 6.B.237.237; 6.B.237.238; 6.B.237.239; 6.B.237.154; 6.B.237.157;
6.B.237.166; 6.B.237.169; 6.B.237.172; 6.B.237.175; 6.B.237.240; 6.B.237.244; 6.B.238.228;
6.B.238.229; 6.B.238.230; 6.B.238.231; 6.B.238.236; 6.B.238.237; 6.B.238.238; 6.B.238.239;
20 6.B.238.154; 6.B.238.157; 6.B.238.166; 6.B.238.169; 6.B.238.172; 6.B.238.175; 6.B.238.240;
6.B.238.244; 6.B.239.228; 6.B.239.229; 6.B.239.230; 6.B.239.231; 6.B.239.236; 6.B.239.237;
6.B.239.238; 6.B.239.239; 6.B.239.154; 6.B.239.157; 6.B.239.166; 6.B.239.169; 6.B.239.172;
6.B.239.175; 6.B.239.240; 6.B.239.244; 6.B.154.228; 6.B.154.229; 6.B.154.230; 6.B.154.231;
6.B.154.236; 6.B.154.237; 6.B.154.238; 6.B.154.239; 6.B.154.154; 6.B.154.157; 6.B.154.166;
25 6.B.154.169; 6.B.154.172; 6.B.154.175; 6.B.154.240; 6.B.154.244; 6.B.157.228; 6.B.157.229;
6.B.157.230; 6.B.157.231; 6.B.157.236; 6.B.157.237; 6.B.157.238; 6.B.157.239; 6.B.157.154;
6.B.157.157; 6.B.157.166; 6.B.157.169; 6.B.157.172; 6.B.157.175; 6.B.157.240; 6.B.157.244;
6.B.166.228; 6.B.166.229; 6.B.166.230; 6.B.166.231; 6.B.166.236; 6.B.166.237; 6.B.166.238;
6.B.166.239; 6.B.166.154; 6.B.166.157; 6.B.166.166; 6.B.166.169; 6.B.166.172; 6.B.166.175;
30 6.B.166.240; 6.B.166.244; 6.B.169.228; 6.B.169.229; 6.B.169.230; 6.B.169.231; 6.B.169.236;
6.B.169.237; 6.B.169.238; 6.B.169.239; 6.B.169.154; 6.B.169.157; 6.B.169.166; 6.B.169.169;
6.B.169.172; 6.B.169.175; 6.B.169.240; 6.B.169.244; 6.B.172.228; 6.B.172.229; 6.B.172.230;
6.B.172.231; 6.B.172.236; 6.B.172.237; 6.B.172.238; 6.B.172.239; 6.B.172.154; 6.B.172.157;
6.B.172.166; 6.B.172.169; 6.B.172.172; 6.B.172.175; 6.B.172.240; 6.B.172.244; 6.B.175.228;
35 6.B.175.229; 6.B.175.230; 6.B.175.231; 6.B.175.236; 6.B.175.237; 6.B.175.238; 6.B.175.239;
6.B.175.154; 6.B.175.157; 6.B.175.166; 6.B.175.169; 6.B.175.172; 6.B.175.175; 6.B.175.240;
6.B.175.244; 6.B.240.228; 6.B.240.229; 6.B.240.230; 6.B.240.231; 6.B.240.236; 6.B.240.237;
6.B.240.238; 6.B.240.239; 6.B.240.154; 6.B.240.157; 6.B.240.166; 6.B.240.169; 6.B.240.172;
6.B.240.175; 6.B.240.240; 6.B.240.244; 6.B.244.228; 6.B.244.229; 6.B.244.230; 6.B.244.231;
40 6.B.244.236; 6.B.244.237; 6.B.244.238; 6.B.244.239; 6.B.244.154; 6.B.244.157; 6.B.244.166;
6.B.244.169; 6.B.244.172; 6.B.244.175; 6.B.244.240; 6.B.244.244;

Prodrugs of 6.D

- 45 6.D.228.228; 6.D.228.229; 6.D.228.230; 6.D.228.231; 6.D.228.236; 6.D.228.237;
6.D.228.238; 6.D.228.239; 6.D.228.154; 6.D.228.157; 6.D.228.166; 6.D.228.169;
6.D.228.172; 6.D.228.175; 6.D.228.240; 6.D.228.244; 6.D.229.228; 6.D.229.229;

- 6.D.229.230; 6.D.229.231; 6.D.229.236; 6.D.229.237; 6.D.229.238; 6.D.229.239;
 6.D.229.154; 6.D.229.157; 6.D.229.166; 6.D.229.169; 6.D.229.172; 6.D.229.175;
 6.D.229.240; 6.D.229.244; 6.D.230.228; 6.D.230.229; 6.D.230.230; 6.D.230.231;
 6.D.230.236; 6.D.230.237; 6.D.230.238; 6.D.230.239; 6.D.230.154; 6.D.230.157;
 5 6.D.230.166; 6.D.230.169; 6.D.230.172; 6.D.230.175; 6.D.230.240; 6.D.230.244;
 6.D.231.228; 6.D.231.229; 6.D.231.230; 6.D.231.231; 6.D.231.236; 6.D.231.237;
 6.D.231.238; 6.D.231.239; 6.D.231.154; 6.D.231.157; 6.D.231.166; 6.D.231.169;
 6.D.231.172; 6.D.231.175; 6.D.231.240; 6.D.231.244; 6.D.236.228; 6.D.236.229;
 6.D.236.230; 6.D.236.231; 6.D.236.236; 6.D.236.237; 6.D.236.238; 6.D.236.239;
 10 6.D.236.154; 6.D.236.157; 6.D.236.166; 6.D.236.169; 6.D.236.172; 6.D.236.175;
 6.D.236.240; 6.D.236.244; 6.D.237.228; 6.D.237.229; 6.D.237.230; 6.D.237.231;
 6.D.237.236; 6.D.237.237; 6.D.237.238; 6.D.237.239; 6.D.237.154; 6.D.237.157;
 6.D.237.166; 6.D.237.169; 6.D.237.172; 6.D.237.175; 6.D.237.240; 6.D.237.244;
 6.D.238.228; 6.D.238.229; 6.D.238.230; 6.D.238.231; 6.D.238.236; 6.D.238.237;
 15 6.D.238.238; 6.D.238.239; 6.D.238.154; 6.D.238.157; 6.D.238.166; 6.D.238.169;
 6.D.238.172; 6.D.238.175; 6.D.238.240; 6.D.238.244; 6.D.239.228; 6.D.239.229;
 6.D.239.230; 6.D.239.231; 6.D.239.236; 6.D.239.237; 6.D.239.238; 6.D.239.239;
 6.D.239.154; 6.D.239.157; 6.D.239.166; 6.D.239.169; 6.D.239.172; 6.D.239.175;
 6.D.239.240; 6.D.239.244; 6.D.154.228; 6.D.154.229; 6.D.154.230; 6.D.154.231;
 20 6.D.154.236; 6.D.154.237; 6.D.154.238; 6.D.154.239; 6.D.154.154; 6.D.154.157;
 6.D.154.166; 6.D.154.169; 6.D.154.172; 6.D.154.175; 6.D.154.240; 6.D.154.244;
 6.D.157.228; 6.D.157.229; 6.D.157.230; 6.D.157.231; 6.D.157.236; 6.D.157.237;
 6.D.157.238; 6.D.157.239; 6.D.157.154; 6.D.157.157; 6.D.157.166; 6.D.157.169;
 6.D.157.172; 6.D.157.175; 6.D.157.240; 6.D.157.244; 6.D.166.228; 6.D.166.229;
 25 6.D.166.230; 6.D.166.231; 6.D.166.236; 6.D.166.237; 6.D.166.238; 6.D.166.239;
 6.D.166.154; 6.D.166.157; 6.D.166.166; 6.D.166.169; 6.D.166.172; 6.D.166.175;
 6.D.166.240; 6.D.166.244; 6.D.169.228; 6.D.169.229; 6.D.169.230; 6.D.169.231;
 6.D.169.236; 6.D.169.237; 6.D.169.238; 6.D.169.239; 6.D.169.154; 6.D.169.157;
 6.D.169.166; 6.D.169.169; 6.D.169.172; 6.D.169.175; 6.D.169.240; 6.D.169.244;
 30 6.D.172.228; 6.D.172.229; 6.D.172.230; 6.D.172.231; 6.D.172.236; 6.D.172.237;
 6.D.172.238; 6.D.172.239; 6.D.172.154; 6.D.172.157; 6.D.172.166; 6.D.172.169;
 6.D.172.172; 6.D.172.175; 6.D.172.240; 6.D.172.244; 6.D.175.228; 6.D.175.229;
 6.D.175.230; 6.D.175.231; 6.D.175.236; 6.D.175.237; 6.D.175.238; 6.D.175.239;
 6.D.175.154; 6.D.175.157; 6.D.175.166; 6.D.175.169; 6.D.175.172; 6.D.175.175;
 35 6.D.175.240; 6.D.175.244; 6.D.240.228; 6.D.240.229; 6.D.240.230; 6.D.240.231;
 6.D.240.236; 6.D.240.237; 6.D.240.238; 6.D.240.239; 6.D.240.154; 6.D.240.157;
 6.D.240.166; 6.D.240.169; 6.D.240.172; 6.D.240.175; 6.D.240.240; 6.D.240.244;
 6.D.244.228; 6.D.244.229; 6.D.244.230; 6.D.244.231; 6.D.244.236; 6.D.244.237;
 6.D.244.238; 6.D.244.239; 6.D.244.154; 6.D.244.157; 6.D.244.166; 6.D.244.169;
 40 6.D.244.172; 6.D.244.175; 6.D.244.240; 6.D.244.244;

Prodrugs of 6.E

- 6.E.228.228; 6.E.228.229; 6.E.228.230; 6.E.228.231; 6.E.228.236; 6.E.228.237;
 6.E.228.238; 6.E.228.239; 6.E.228.154; 6.E.228.157; 6.E.228.166; 6.E.228.169; 6.E.228.172;
 45 6.E.228.175; 6.E.228.240; 6.E.228.244; 6.E.229.228; 6.E.229.229; 6.E.229.230; 6.E.229.231;
 6.E.229.236; 6.E.229.237; 6.E.229.238; 6.E.229.239; 6.E.229.154; 6.E.229.157; 6.E.229.166;

6.E.229.169; 6.E.229.172; 6.E.229.175; 6.E.229.240; 6.E.229.244; 6.E.230.228; 6.E.230.229;
 6.E.230.230; 6.E.230.231; 6.E.230.236; 6.E.230.237; 6.E.230.238; 6.E.230.239; 6.E.230.154;
 6.E.230.157; 6.E.230.166; 6.E.230.169; 6.E.230.172; 6.E.230.175; 6.E.230.240; 6.E.230.244;
 6.E.231.228; 6.E.231.229; 6.E.231.230; 6.E.231.231; 6.E.231.236; 6.E.231.237; 6.E.231.238;
 5 6.E.231.239; 6.E.231.154; 6.E.231.157; 6.E.231.166; 6.E.231.169; 6.E.231.172; 6.E.231.175;
 6.E.231.240; 6.E.231.244; 6.E.236.228; 6.E.236.229; 6.E.236.230; 6.E.236.231; 6.E.236.236;
 6.E.236.237; 6.E.236.238; 6.E.236.239; 6.E.236.154; 6.E.236.157; 6.E.236.166; 6.E.236.169;
 6.E.236.172; 6.E.236.175; 6.E.236.240; 6.E.236.244; 6.E.237.228; 6.E.237.229; 6.E.237.230;
 6.E.237.231; 6.E.237.236; 6.E.237.237; 6.E.237.238; 6.E.237.239; 6.E.237.154; 6.E.237.157;
 10 6.E.237.166; 6.E.237.169; 6.E.237.172; 6.E.237.175; 6.E.237.240; 6.E.237.244; 6.E.238.228;
 6.E.238.229; 6.E.238.230; 6.E.238.231; 6.E.238.236; 6.E.238.237; 6.E.238.238; 6.E.238.239;
 6.E.238.154; 6.E.238.157; 6.E.238.166; 6.E.238.169; 6.E.238.172; 6.E.238.175; 6.E.238.240;
 6.E.238.244; 6.E.239.228; 6.E.239.229; 6.E.239.230; 6.E.239.231; 6.E.239.236; 6.E.239.237;
 6.E.239.238; 6.E.239.239; 6.E.239.154; 6.E.239.157; 6.E.239.166; 6.E.239.169; 6.E.239.172;
 15 6.E.239.175; 6.E.239.240; 6.E.239.244; 6.E.154.228; 6.E.154.229; 6.E.154.230; 6.E.154.231;
 6.E.154.236; 6.E.154.237; 6.E.154.238; 6.E.154.239; 6.E.154.154; 6.E.154.157; 6.E.154.166;
 6.E.154.169; 6.E.154.172; 6.E.154.175; 6.E.154.240; 6.E.154.244; 6.E.157.228; 6.E.157.229;
 6.E.157.230; 6.E.157.231; 6.E.157.236; 6.E.157.237; 6.E.157.238; 6.E.157.239; 6.E.157.154;
 6.E.157.157; 6.E.157.166; 6.E.157.169; 6.E.157.172; 6.E.157.175; 6.E.157.240; 6.E.157.244;
 20 6.E.166.228; 6.E.166.229; 6.E.166.230; 6.E.166.231; 6.E.166.236; 6.E.166.237; 6.E.166.238;
 6.E.166.239; 6.E.166.154; 6.E.166.157; 6.E.166.166; 6.E.166.169; 6.E.166.172; 6.E.166.175;
 6.E.166.240; 6.E.166.244; 6.E.169.228; 6.E.169.229; 6.E.169.230; 6.E.169.231; 6.E.169.236;
 6.E.169.237; 6.E.169.238; 6.E.169.239; 6.E.169.154; 6.E.169.157; 6.E.169.166; 6.E.169.169;
 6.E.169.172; 6.E.169.175; 6.E.169.240; 6.E.169.244; 6.E.172.228; 6.E.172.229; 6.E.172.230;
 25 6.E.172.231; 6.E.172.236; 6.E.172.237; 6.E.172.238; 6.E.172.239; 6.E.172.154; 6.E.172.157;
 6.E.172.166; 6.E.172.169; 6.E.172.172; 6.E.172.175; 6.E.172.240; 6.E.172.244; 6.E.175.228;
 6.E.175.229; 6.E.175.230; 6.E.175.231; 6.E.175.236; 6.E.175.237; 6.E.175.238; 6.E.175.239;
 6.E.175.154; 6.E.175.157; 6.E.175.166; 6.E.175.169; 6.E.175.172; 6.E.175.175; 6.E.175.240;
 6.E.175.244; 6.E.240.228; 6.E.240.229; 6.E.240.230; 6.E.240.231; 6.E.240.236; 6.E.240.237;
 30 6.E.240.238; 6.E.240.239; 6.E.240.154; 6.E.240.157; 6.E.240.166; 6.E.240.169; 6.E.240.172;
 6.E.240.175; 6.E.240.240; 6.E.240.244; 6.E.244.228; 6.E.244.229; 6.E.244.230; 6.E.244.231;
 6.E.244.236; 6.E.244.237; 6.E.244.238; 6.E.244.239; 6.E.244.154; 6.E.244.157; 6.E.244.166;
 6.E.244.169; 6.E.244.172; 6.E.244.175; 6.E.244.240; 6.E.244.244;

35 Prodrugs of 6.G

6.G.228.228; 6.G.228.229; 6.G.228.230; 6.G.228.231; 6.G.228.236; 6.G.228.237;
 6.G.228.238; 6.G.228.239; 6.G.228.154; 6.G.228.157; 6.G.228.166; 6.G.228.169;
 6.G.228.172; 6.G.228.175; 6.G.228.240; 6.G.228.244; 6.G.229.228; 6.G.229.229;
 6.G.229.230; 6.G.229.231; 6.G.229.236; 6.G.229.237; 6.G.229.238; 6.G.229.239;
 40 6.G.229.154; 6.G.229.157; 6.G.229.166; 6.G.229.169; 6.G.229.172; 6.G.229.175;
 6.G.229.240; 6.G.229.244; 6.G.230.228; 6.G.230.229; 6.G.230.230; 6.G.230.231;
 6.G.230.236; 6.G.230.237; 6.G.230.238; 6.G.230.239; 6.G.230.154; 6.G.230.157;
 6.G.230.166; 6.G.230.169; 6.G.230.172; 6.G.230.175; 6.G.230.240; 6.G.230.244;
 6.G.231.228; 6.G.231.229; 6.G.231.230; 6.G.231.231; 6.G.231.236; 6.G.231.237;
 45 6.G.231.238; 6.G.231.239; 6.G.231.154; 6.G.231.157; 6.G.231.166; 6.G.231.169;
 6.G.231.172; 6.G.231.175; 6.G.231.240; 6.G.231.244; 6.G.236.228; 6.G.236.229;

6.G.236.230; 6.G.236.231; 6.G.236.236; 6.G.236.237; 6.G.236.238; 6.G.236.239;
 6.G.236.154; 6.G.236.157; 6.G.236.166; 6.G.236.169; 6.G.236.172; 6.G.236.175;
 6.G.236.240; 6.G.236.244; 6.G.237.228; 6.G.237.229; 6.G.237.230; 6.G.237.231;
 6.G.237.236; 6.G.237.237; 6.G.237.238; 6.G.237.239; 6.G.237.154; 6.G.237.157;
 5 6.G.237.166; 6.G.237.169; 6.G.237.172; 6.G.237.175; 6.G.237.240; 6.G.237.244;
 6.G.238.228; 6.G.238.229; 6.G.238.230; 6.G.238.231; 6.G.238.236; 6.G.238.237;
 6.G.238.238; 6.G.238.239; 6.G.238.154; 6.G.238.157; 6.G.238.166; 6.G.238.169;
 6.G.238.172; 6.G.238.175; 6.G.238.240; 6.G.238.244; 6.G.239.228; 6.G.239.229;
 6.G.239.230; 6.G.239.231; 6.G.239.236; 6.G.239.237; 6.G.239.238; 6.G.239.239;
 10 6.G.239.154; 6.G.239.157; 6.G.239.166; 6.G.239.169; 6.G.239.172; 6.G.239.175;
 6.G.239.240; 6.G.239.244; 6.G.154.228; 6.G.154.229; 6.G.154.230; 6.G.154.231;
 6.G.154.236; 6.G.154.237; 6.G.154.238; 6.G.154.239; 6.G.154.154; 6.G.154.157;
 6.G.154.166; 6.G.154.169; 6.G.154.172; 6.G.154.175; 6.G.154.240; 6.G.154.244;
 6.G.157.228; 6.G.157.229; 6.G.157.230; 6.G.157.231; 6.G.157.236; 6.G.157.237;
 15 6.G.157.238; 6.G.157.239; 6.G.157.154; 6.G.157.157; 6.G.157.166; 6.G.157.169;
 6.G.157.172; 6.G.157.175; 6.G.157.240; 6.G.157.244; 6.G.166.228; 6.G.166.229;
 6.G.166.230; 6.G.166.231; 6.G.166.236; 6.G.166.237; 6.G.166.238; 6.G.166.239;
 6.G.166.154; 6.G.166.157; 6.G.166.166; 6.G.166.169; 6.G.166.172; 6.G.166.175;
 6.G.166.240; 6.G.166.244; 6.G.169.228; 6.G.169.229; 6.G.169.230; 6.G.169.231;
 20 6.G.169.236; 6.G.169.237; 6.G.169.238; 6.G.169.239; 6.G.169.154; 6.G.169.157;
 6.G.169.166; 6.G.169.169; 6.G.169.172; 6.G.169.175; 6.G.169.240; 6.G.169.244;
 6.G.172.228; 6.G.172.229; 6.G.172.230; 6.G.172.231; 6.G.172.236; 6.G.172.237;
 6.G.172.238; 6.G.172.239; 6.G.172.154; 6.G.172.157; 6.G.172.166; 6.G.172.169;
 6.G.172.172; 6.G.172.175; 6.G.172.240; 6.G.172.244; 6.G.175.228; 6.G.175.229;
 25 6.G.175.230; 6.G.175.231; 6.G.175.236; 6.G.175.237; 6.G.175.238; 6.G.175.239;
 6.G.175.154; 6.G.175.157; 6.G.175.166; 6.G.175.169; 6.G.175.172; 6.G.175.175;
 6.G.175.240; 6.G.175.244; 6.G.240.228; 6.G.240.229; 6.G.240.230; 6.G.240.231;
 6.G.240.236; 6.G.240.237; 6.G.240.238; 6.G.240.239; 6.G.240.154; 6.G.240.157;
 6.G.240.166; 6.G.240.169; 6.G.240.172; 6.G.240.175; 6.G.240.240; 6.G.240.244;
 30 6.G.244.228; 6.G.244.229; 6.G.244.230; 6.G.244.231; 6.G.244.236; 6.G.244.237;
 6.G.244.238; 6.G.244.239; 6.G.244.154; 6.G.244.157; 6.G.244.166; 6.G.244.169;
 6.G.244.172; 6.G.244.175; 6.G.244.240; 6.G.244.244;

Prodrugs of 6.I

35 6.I.228.228; 6.I.228.229; 6.I.228.230; 6.I.228.231; 6.I.228.236; 6.I.228.237; 6.I.228.238;
 6.I.228.239; 6.I.228.154; 6.I.228.157; 6.I.228.166; 6.I.228.169; 6.I.228.172; 6.I.228.175;
 6.I.228.240; 6.I.228.244; 6.I.229.228; 6.I.229.229; 6.I.229.230; 6.I.229.231; 6.I.229.236;
 6.I.229.237; 6.I.229.238; 6.I.229.239; 6.I.229.154; 6.I.229.157; 6.I.229.166; 6.I.229.169;
 6.I.229.172; 6.I.229.175; 6.I.229.240; 6.I.229.244; 6.I.230.228; 6.I.230.229; 6.I.230.230;
 40 6.I.230.231; 6.I.230.236; 6.I.230.237; 6.I.230.238; 6.I.230.239; 6.I.230.154; 6.I.230.157;
 6.I.230.166; 6.I.230.169; 6.I.230.172; 6.I.230.175; 6.I.230.240; 6.I.230.244; 6.I.231.228;
 6.I.231.229; 6.I.231.230; 6.I.231.231; 6.I.231.236; 6.I.231.237; 6.I.231.238; 6.I.231.239;
 6.I.231.154; 6.I.231.157; 6.I.231.166; 6.I.231.169; 6.I.231.172; 6.I.231.175; 6.I.231.240;
 6.I.231.244; 6.I.236.228; 6.I.236.229; 6.I.236.230; 6.I.236.231; 6.I.236.236; 6.I.236.237;
 45 6.I.236.238; 6.I.236.239; 6.I.236.154; 6.I.236.157; 6.I.236.166; 6.I.236.169; 6.I.236.172;
 6.I.236.175; 6.I.236.240; 6.I.236.244; 6.I.237.228; 6.I.237.229; 6.I.237.230; 6.I.237.231;

6.I.237.236; 6.I.237.237; 6.I.237.238; 6.I.237.239; 6.I.237.154; 6.I.237.157; 6.I.237.166;
 6.I.237.169; 6.I.237.172; 6.I.237.175; 6.I.237.240; 6.I.237.244; 6.I.238.228; 6.I.238.229;
 6.I.238.230; 6.I.238.231; 6.I.238.236; 6.I.238.237; 6.I.238.238; 6.I.238.239; 6.I.238.154;
 6.I.238.157; 6.I.238.166; 6.I.238.169; 6.I.238.172; 6.I.238.175; 6.I.238.240; 6.I.238.244;
 5 6.I.239.228; 6.I.239.229; 6.I.239.230; 6.I.239.231; 6.I.239.236; 6.I.239.237; 6.I.239.238;
 6.I.239.239; 6.I.239.154; 6.I.239.157; 6.I.239.166; 6.I.239.169; 6.I.239.172; 6.I.239.175;
 6.I.239.240; 6.I.239.244; 6.I.154.228; 6.I.154.229; 6.I.154.230; 6.I.154.231; 6.I.154.236;
 6.I.154.237; 6.I.154.238; 6.I.154.239; 6.I.154.154; 6.I.154.157; 6.I.154.166; 6.I.154.169;
 6.I.154.172; 6.I.154.175; 6.I.154.240; 6.I.154.244; 6.I.157.228; 6.I.157.229; 6.I.157.230;
 10 6.I.157.231; 6.I.157.236; 6.I.157.237; 6.I.157.238; 6.I.157.239; 6.I.157.154; 6.I.157.157;
 6.I.157.166; 6.I.157.169; 6.I.157.172; 6.I.157.175; 6.I.157.240; 6.I.157.244; 6.I.166.228;
 6.I.166.229; 6.I.166.230; 6.I.166.231; 6.I.166.236; 6.I.166.237; 6.I.166.238; 6.I.166.239;
 6.I.166.154; 6.I.166.157; 6.I.166.166; 6.I.166.169; 6.I.166.172; 6.I.166.175; 6.I.166.240;
 6.I.166.244; 6.I.169.228; 6.I.169.229; 6.I.169.230; 6.I.169.231; 6.I.169.236; 6.I.169.237;
 15 6.I.169.238; 6.I.169.239; 6.I.169.154; 6.I.169.157; 6.I.169.166; 6.I.169.169; 6.I.169.172;
 6.I.169.175; 6.I.169.240; 6.I.169.244; 6.I.172.228; 6.I.172.229; 6.I.172.230; 6.I.172.231;
 6.I.172.236; 6.I.172.237; 6.I.172.238; 6.I.172.239; 6.I.172.154; 6.I.172.157; 6.I.172.166;
 6.I.172.169; 6.I.172.172; 6.I.172.175; 6.I.172.240; 6.I.172.244; 6.I.175.228; 6.I.175.229;
 6.I.175.230; 6.I.175.231; 6.I.175.236; 6.I.175.237; 6.I.175.238; 6.I.175.239; 6.I.175.154;
 20 6.I.175.157; 6.I.175.166; 6.I.175.169; 6.I.175.172; 6.I.175.175; 6.I.175.240; 6.I.175.244;
 6.I.240.228; 6.I.240.229; 6.I.240.230; 6.I.240.231; 6.I.240.236; 6.I.240.237; 6.I.240.238;
 6.I.240.239; 6.I.240.154; 6.I.240.157; 6.I.240.166; 6.I.240.169; 6.I.240.172; 6.I.240.175;
 6.I.240.240; 6.I.240.244; 6.I.244.228; 6.I.244.229; 6.I.244.230; 6.I.244.231; 6.I.244.236;
 6.I.244.237; 6.I.244.238; 6.I.244.239; 6.I.244.154; 6.I.244.157; 6.I.244.166; 6.I.244.169;
 25 6.I.244.172; 6.I.244.175; 6.I.244.240; 6.I.244.244;

Prodrugs of 6.I

6.J.228.228; 6.J.228.229; 6.J.228.230; 6.J.228.231; 6.J.228.236; 6.J.228.237; 6.J.228.238;
 6.J.228.239; 6.J.228.154; 6.J.228.157; 6.J.228.166; 6.J.228.169; 6.J.228.172; 6.J.228.175;
 30 6.J.228.240; 6.J.228.244; 6.J.229.228; 6.J.229.229; 6.J.229.230; 6.J.229.231; 6.J.229.236;
 6.J.229.237; 6.J.229.238; 6.J.229.239; 6.J.229.154; 6.J.229.157; 6.J.229.166; 6.J.229.169;
 6.J.229.172; 6.J.229.175; 6.J.229.240; 6.J.229.244; 6.J.230.228; 6.J.230.229; 6.J.230.230;
 6.J.230.231; 6.J.230.236; 6.J.230.237; 6.J.230.238; 6.J.230.239; 6.J.230.154; 6.J.230.157;
 6.J.230.166; 6.J.230.169; 6.J.230.172; 6.J.230.175; 6.J.230.240; 6.J.230.244; 6.J.231.228;
 35 6.J.231.229; 6.J.231.230; 6.J.231.231; 6.J.231.236; 6.J.231.237; 6.J.231.238; 6.J.231.239;
 6.J.231.154; 6.J.231.157; 6.J.231.166; 6.J.231.169; 6.J.231.172; 6.J.231.175; 6.J.231.240;
 6.J.231.244; 6.J.236.228; 6.J.236.229; 6.J.236.230; 6.J.236.231; 6.J.236.236; 6.J.236.237;
 6.J.236.238; 6.J.236.239; 6.J.236.154; 6.J.236.157; 6.J.236.166; 6.J.236.169; 6.J.236.172;
 6.J.236.175; 6.J.236.240; 6.J.236.244; 6.J.237.228; 6.J.237.229; 6.J.237.230; 6.J.237.231;
 40 6.J.237.236; 6.J.237.237; 6.J.237.238; 6.J.237.239; 6.J.237.154; 6.J.237.157; 6.J.237.166;
 6.J.237.169; 6.J.237.172; 6.J.237.175; 6.J.237.240; 6.J.237.244; 6.J.238.228; 6.J.238.229;
 6.J.238.230; 6.J.238.231; 6.J.238.236; 6.J.238.237; 6.J.238.238; 6.J.238.239; 6.J.238.154;
 6.J.238.157; 6.J.238.166; 6.J.238.169; 6.J.238.172; 6.J.238.175; 6.J.238.240; 6.J.238.244;
 6.J.239.228; 6.J.239.229; 6.J.239.230; 6.J.239.231; 6.J.239.236; 6.J.239.237; 6.J.239.238;
 45 6.J.239.239; 6.J.239.154; 6.J.239.157; 6.J.239.166; 6.J.239.169; 6.J.239.172; 6.J.239.175;
 6.J.239.240; 6.J.239.244; 6.J.154.228; 6.J.154.229; 6.J.154.230; 6.J.154.231; 6.J.154.236;

- 6.J.154.237; 6.J.154.238; 6.J.154.239; 6.J.154.154; 6.J.154.157; 6.J.154.166; 6.J.154.169;
 6.J.154.172; 6.J.154.175; 6.J.154.240; 6.J.154.244; 6.J.157.228; 6.J.157.229; 6.J.157.230;
 6.J.157.231; 6.J.157.236; 6.J.157.237; 6.J.157.238; 6.J.157.239; 6.J.157.154; 6.J.157.157;
 6.J.157.166; 6.J.157.169; 6.J.157.172; 6.J.157.175; 6.J.157.240; 6.J.157.244; 6.J.166.228;
 5 6.J.166.229; 6.J.166.230; 6.J.166.231; 6.J.166.236; 6.J.166.237; 6.J.166.238; 6.J.166.239;
 6.J.166.154; 6.J.166.157; 6.J.166.166; 6.J.166.169; 6.J.166.172; 6.J.166.175; 6.J.166.240;
 6.J.166.244; 6.J.169.228; 6.J.169.229; 6.J.169.230; 6.J.169.231; 6.J.169.236; 6.J.169.237;
 6.J.169.238; 6.J.169.239; 6.J.169.154; 6.J.169.157; 6.J.169.166; 6.J.169.169; 6.J.169.172;
 6.J.169.175; 6.J.169.240; 6.J.169.244; 6.J.172.228; 6.J.172.229; 6.J.172.230; 6.J.172.231;
 10 6.J.172.236; 6.J.172.237; 6.J.172.238; 6.J.172.239; 6.J.172.154; 6.J.172.157; 6.J.172.166;
 6.J.172.169; 6.J.172.172; 6.J.172.175; 6.J.172.240; 6.J.172.244; 6.J.175.228; 6.J.175.229;
 6.J.175.230; 6.J.175.231; 6.J.175.236; 6.J.175.237; 6.J.175.238; 6.J.175.239; 6.J.175.154;
 6.J.175.157; 6.J.175.166; 6.J.175.169; 6.J.175.172; 6.J.175.175; 6.J.175.240; 6.J.175.244;
 6.J.240.228; 6.J.240.229; 6.J.240.230; 6.J.240.231; 6.J.240.236; 6.J.240.237; 6.J.240.238;
 15 6.J.240.239; 6.J.240.154; 6.J.240.157; 6.J.240.166; 6.J.240.169; 6.J.240.172; 6.J.240.175;
 6.J.240.240; 6.J.240.244; 6.J.244.228; 6.J.244.229; 6.J.244.230; 6.J.244.231; 6.J.244.236;
 6.J.244.237; 6.J.244.238; 6.J.244.239; 6.J.244.154; 6.J.244.157; 6.J.244.166; 6.J.244.169;
 6.J.244.172; 6.J.244.175; 6.J.244.240; 6.J.244.244;
- 20 Prodrugs of 6.L
 6.L.228.228; 6.L.228.229; 6.L.228.230; 6.L.228.231; 6.L.228.236; 6.L.228.237;
 6.L.228.238; 6.L.228.239; 6.L.228.154; 6.L.228.157; 6.L.228.166; 6.L.228.169; 6.L.228.172;
 6.L.228.175; 6.L.228.240; 6.L.228.244; 6.L.229.228; 6.L.229.229; 6.L.229.230; 6.L.229.231;
 6.L.229.236; 6.L.229.237; 6.L.229.238; 6.L.229.239; 6.L.229.154; 6.L.229.157; 6.L.229.166;
 25 6.L.229.169; 6.L.229.172; 6.L.229.175; 6.L.229.240; 6.L.229.244; 6.L.230.228; 6.L.230.229;
 6.L.230.230; 6.L.230.231; 6.L.230.236; 6.L.230.237; 6.L.230.238; 6.L.230.239; 6.L.230.154;
 6.L.230.157; 6.L.230.166; 6.L.230.169; 6.L.230.172; 6.L.230.175; 6.L.230.240; 6.L.230.244;
 6.L.231.228; 6.L.231.229; 6.L.231.230; 6.L.231.231; 6.L.231.236; 6.L.231.237; 6.L.231.238;
 6.L.231.239; 6.L.231.154; 6.L.231.157; 6.L.231.166; 6.L.231.169; 6.L.231.172; 6.L.231.175;
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 10 6.L.244.236; 6.L.244.237; 6.L.244.238; 6.L.244.239; 6.L.244.154; 6.L.244.157; 6.L.244.166;
 6.L.244.169; 6.L.244.172; 6.L.244.175; 6.L.244.240; 6.L.244.244;

Prodrugs of 6.O

6.O.228.228; 6.O.228.229; 6.O.228.230; 6.O.228.231; 6.O.228.236; 6.O.228.237;
 15 6.O.228.238; 6.O.228.239; 6.O.228.154; 6.O.228.157; 6.O.228.166; 6.O.228.169;
 6.O.228.172; 6.O.228.175; 6.O.228.240; 6.O.228.244; 6.O.229.228; 6.O.229.229;
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 6.O.229.154; 6.O.229.157; 6.O.229.166; 6.O.229.169; 6.O.229.172; 6.O.229.175;
 6.O.229.240; 6.O.229.244; 6.O.230.228; 6.O.230.229; 6.O.230.230; 6.O.230.231;
 20 6.O.230.236; 6.O.230.237; 6.O.230.238; 6.O.230.239; 6.O.230.154; 6.O.230.157;
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 40 6.O.157.172; 6.O.157.175; 6.O.157.240; 6.O.157.244; 6.O.166.228; 6.O.166.229;
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 5 6.O.175.240; 6.O.175.244; 6.O.240.228; 6.O.240.229; 6.O.240.230; 6.O.240.231;
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 10 6.O.244.172; 6.O.244.175; 6.O.244.240; 6.O.244.244;

Prodrugs of 6.P

6.P.228.228; 6.P.228.229; 6.P.228.230; 6.P.228.231; 6.P.228.236; 6.P.228.237;
 6.P.228.238; 6.P.228.239; 6.P.228.154; 6.P.228.157; 6.P.228.166; 6.P.228.169; 6.P.228.172;
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 6.P.230.230; 6.P.230.231; 6.P.230.236; 6.P.230.237; 6.P.230.238; 6.P.230.239; 6.P.230.154;
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 20 6.P.231.228; 6.P.231.229; 6.P.231.230; 6.P.231.231; 6.P.231.236; 6.P.231.237; 6.P.231.238;
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 6.P.237.166; 6.P.237.169; 6.P.237.172; 6.P.237.175; 6.P.237.240; 6.P.237.244; 6.P.238.228;
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 6.P.175.154; 6.P.175.157; 6.P.175.166; 6.P.175.169; 6.P.175.172; 6.P.175.175; 6.P.175.240;
 45 6.P.175.244; 6.P.240.228; 6.P.240.229; 6.P.240.230; 6.P.240.231; 6.P.240.236; 6.P.240.237;
 6.P.240.238; 6.P.240.239; 6.P.240.154; 6.P.240.157; 6.P.240.166; 6.P.240.169; 6.P.240.172;

6.P.240.175; 6.P.240.240; 6.P.240.244; 6.P.244.228; 6.P.244.229; 6.P.244.230; 6.P.244.231;
 6.P.244.236; 6.P.244.237; 6.P.244.238; 6.P.244.239; 6.P.244.154; 6.P.244.157; 6.P.244.166;
 6.P.244.169; 6.P.244.172; 6.P.244.175; 6.P.244.240; 6.P.244.244;

5 Prodrugs of 6.U

- 6.U.228.228; 6.U.228.229; 6.U.228.230; 6.U.228.231; 6.U.228.236; 6.U.228.237;
 6.U.228.238; 6.U.228.239; 6.U.228.154; 6.U.228.157; 6.U.228.166; 6.U.228.169;
 6.U.228.172; 6.U.228.175; 6.U.228.240; 6.U.228.244; 6.U.229.228; 6.U.229.229;
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 10 6.U.229.154; 6.U.229.157; 6.U.229.166; 6.U.229.169; 6.U.229.172; 6.U.229.175;
 6.U.229.240; 6.U.229.244; 6.U.230.228; 6.U.230.229; 6.U.230.230; 6.U.230.231;
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 15 6.U.231.238; 6.U.231.239; 6.U.231.154; 6.U.231.157; 6.U.231.166; 6.U.231.169;
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 6.U.238.238; 6.U.238.239; 6.U.238.154; 6.U.238.157; 6.U.238.166; 6.U.238.169;
 6.U.238.172; 6.U.238.175; 6.U.238.240; 6.U.238.244; 6.U.239.228; 6.U.239.229;
 25 6.U.239.230; 6.U.239.231; 6.U.239.236; 6.U.239.237; 6.U.239.238; 6.U.239.239;
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 6.U.157.238; 6.U.157.239; 6.U.157.154; 6.U.157.157; 6.U.157.166; 6.U.157.169;
 6.U.157.172; 6.U.157.175; 6.U.157.240; 6.U.157.244; 6.U.166.228; 6.U.166.229;
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 6.U.240.236; 6.U.240.237; 6.U.240.238; 6.U.240.239; 6.U.240.154; 6.U.240.157;
 45 6.U.240.166; 6.U.240.169; 6.U.240.172; 6.U.240.175; 6.U.240.240; 6.U.240.244;
 6.U.244.228; 6.U.244.229; 6.U.244.230; 6.U.244.231; 6.U.244.236; 6.U.244.237;

6.U.244.238; 6.U.244.239; 6.U.244.154; 6.U.244.157; 6.U.244.166; 6.U.244.169;
6.U.244.172; 6.U.244.175; 6.U.244.240; 6.U.244.244;

Prodrugs of 6.W

- 5 6.W.228.228; 6.W.228.229; 6.W.228.230; 6.W.228.231; 6.W.228.236; 6.W.228.237;
6.W.228.238; 6.W.228.239; 6.W.228.154; 6.W.228.157; 6.W.228.166; 6.W.228.169;
6.W.228.172; 6.W.228.175; 6.W.228.240; 6.W.228.244; 6.W.229.228; 6.W.229.229;
6.W.229.230; 6.W.229.231; 6.W.229.236; 6.W.229.237; 6.W.229.238; 6.W.229.239;
6.W.229.154; 6.W.229.157; 6.W.229.166; 6.W.229.169; 6.W.229.172; 6.W.229.175;
10 6.W.229.240; 6.W.229.244; 6.W.230.228; 6.W.230.229; 6.W.230.230; 6.W.230.231;
6.W.230.236; 6.W.230.237; 6.W.230.238; 6.W.230.239; 6.W.230.154; 6.W.230.157;
6.W.230.166; 6.W.230.169; 6.W.230.172; 6.W.230.175; 6.W.230.240; 6.W.230.244;
6.W.231.228; 6.W.231.229; 6.W.231.230; 6.W.231.231; 6.W.231.236; 6.W.231.237;
6.W.231.238; 6.W.231.239; 6.W.231.154; 6.W.231.157; 6.W.231.166; 6.W.231.169;
15 6.W.231.172; 6.W.231.175; 6.W.231.240; 6.W.231.244; 6.W.236.228; 6.W.236.229;
6.W.236.230; 6.W.236.231; 6.W.236.236; 6.W.236.237; 6.W.236.238; 6.W.236.239;
6.W.236.154; 6.W.236.157; 6.W.236.166; 6.W.236.169; 6.W.236.172; 6.W.236.175;
6.W.236.240; 6.W.236.244; 6.W.237.228; 6.W.237.229; 6.W.237.230; 6.W.237.231;
6.W.237.236; 6.W.237.237; 6.W.237.238; 6.W.237.239; 6.W.237.154; 6.W.237.157;
20 6.W.237.166; 6.W.237.169; 6.W.237.172; 6.W.237.175; 6.W.237.240; 6.W.237.244;
6.W.238.228; 6.W.238.229; 6.W.238.230; 6.W.238.231; 6.W.238.236; 6.W.238.237;
6.W.238.238; 6.W.238.239; 6.W.238.154; 6.W.238.157; 6.W.238.166; 6.W.238.169;
6.W.238.172; 6.W.238.175; 6.W.238.240; 6.W.238.244; 6.W.239.228; 6.W.239.229;
6.W.239.230; 6.W.239.231; 6.W.239.236; 6.W.239.237; 6.W.239.238; 6.W.239.239;
25 6.W.239.154; 6.W.239.157; 6.W.239.166; 6.W.239.169; 6.W.239.172; 6.W.239.175;
6.W.239.240; 6.W.239.244; 6.W.154.228; 6.W.154.229; 6.W.154.230; 6.W.154.231;
6.W.154.236; 6.W.154.237; 6.W.154.238; 6.W.154.239; 6.W.154.154; 6.W.154.157;
6.W.154.166; 6.W.154.169; 6.W.154.172; 6.W.154.175; 6.W.154.240; 6.W.154.244;
6.W.157.228; 6.W.157.229; 6.W.157.230; 6.W.157.231; 6.W.157.236; 6.W.157.237;
30 6.W.157.238; 6.W.157.239; 6.W.157.154; 6.W.157.157; 6.W.157.166; 6.W.157.169;
6.W.157.172; 6.W.157.175; 6.W.157.240; 6.W.157.244; 6.W.166.228; 6.W.166.229;
6.W.166.230; 6.W.166.231; 6.W.166.236; 6.W.166.237; 6.W.166.238; 6.W.166.239;
6.W.166.154; 6.W.166.157; 6.W.166.166; 6.W.166.169; 6.W.166.172; 6.W.166.175;
6.W.166.240; 6.W.166.244; 6.W.169.228; 6.W.169.229; 6.W.169.230; 6.W.169.231;
35 6.W.169.236; 6.W.169.237; 6.W.169.238; 6.W.169.239; 6.W.169.154; 6.W.169.157;
6.W.169.166; 6.W.169.169; 6.W.169.172; 6.W.169.175; 6.W.169.240; 6.W.169.244;
6.W.172.228; 6.W.172.229; 6.W.172.230; 6.W.172.231; 6.W.172.236; 6.W.172.237;
6.W.172.238; 6.W.172.239; 6.W.172.154; 6.W.172.157; 6.W.172.166; 6.W.172.169;
6.W.172.172; 6.W.172.175; 6.W.172.240; 6.W.172.244; 6.W.175.228; 6.W.175.229;
40 6.W.175.230; 6.W.175.231; 6.W.175.236; 6.W.175.237; 6.W.175.238; 6.W.175.239;
6.W.175.154; 6.W.175.157; 6.W.175.166; 6.W.175.169; 6.W.175.172; 6.W.175.175;
6.W.175.240; 6.W.175.244; 6.W.240.228; 6.W.240.229; 6.W.240.230; 6.W.240.231;
6.W.240.236; 6.W.240.237; 6.W.240.238; 6.W.240.239; 6.W.240.154; 6.W.240.157;
6.W.240.166; 6.W.240.169; 6.W.240.172; 6.W.240.175; 6.W.240.240; 6.W.240.244;
45 6.W.244.228; 6.W.244.229; 6.W.244.230; 6.W.244.231; 6.W.244.236; 6.W.244.237;

6.W.244.238; 6.W.244.239; 6.W.244.154; 6.W.244.157; 6.W.244.166; 6.W.244.169;
6.W.244.172; 6.W.244.175; 6.W.244.240; 6.W.244.244;

Prodrugs of 6.Y

- 5 6.Y.228.228; 6.Y.228.229; 6.Y.228.230; 6.Y.228.231; 6.Y.228.236; 6.Y.228.237;
6.Y.228.238; 6.Y.228.239; 6.Y.228.154; 6.Y.228.157; 6.Y.228.166; 6.Y.228.169;
6.Y.228.172; 6.Y.228.175; 6.Y.228.240; 6.Y.228.244; 6.Y.229.228; 6.Y.229.229;
6.Y.229.230; 6.Y.229.231; 6.Y.229.236; 6.Y.229.237; 6.Y.229.238; 6.Y.229.239;
6.Y.229.154; 6.Y.229.157; 6.Y.229.166; 6.Y.229.169; 6.Y.229.172; 6.Y.229.175;
10 6.Y.229.240; 6.Y.229.244; 6.Y.230.228; 6.Y.230.229; 6.Y.230.230; 6.Y.230.231;
6.Y.230.236; 6.Y.230.237; 6.Y.230.238; 6.Y.230.239; 6.Y.230.154; 6.Y.230.157;
6.Y.230.166; 6.Y.230.169; 6.Y.230.172; 6.Y.230.175; 6.Y.230.240; 6.Y.230.244;
6.Y.231.228; 6.Y.231.229; 6.Y.231.230; 6.Y.231.231; 6.Y.231.236; 6.Y.231.237;
6.Y.231.238; 6.Y.231.239; 6.Y.231.154; 6.Y.231.157; 6.Y.231.166; 6.Y.231.169;
15 6.Y.231.172; 6.Y.231.175; 6.Y.231.240; 6.Y.231.244; 6.Y.236.228; 6.Y.236.229;
6.Y.236.230; 6.Y.236.231; 6.Y.236.236; 6.Y.236.237; 6.Y.236.238; 6.Y.236.239;
6.Y.236.154; 6.Y.236.157; 6.Y.236.166; 6.Y.236.169; 6.Y.236.172; 6.Y.236.175;
6.Y.236.240; 6.Y.236.244; 6.Y.237.228; 6.Y.237.229; 6.Y.237.230; 6.Y.237.231;
6.Y.237.236; 6.Y.237.237; 6.Y.237.238; 6.Y.237.239; 6.Y.237.154; 6.Y.237.157;
20 6.Y.237.166; 6.Y.237.169; 6.Y.237.172; 6.Y.237.175; 6.Y.237.240; 6.Y.237.244;
6.Y.238.228; 6.Y.238.229; 6.Y.238.230; 6.Y.238.231; 6.Y.238.236; 6.Y.238.237;
6.Y.238.238; 6.Y.238.239; 6.Y.238.154; 6.Y.238.157; 6.Y.238.166; 6.Y.238.169;
6.Y.238.172; 6.Y.238.175; 6.Y.238.240; 6.Y.238.244; 6.Y.239.228; 6.Y.239.229;
6.Y.239.230; 6.Y.239.231; 6.Y.239.236; 6.Y.239.237; 6.Y.239.238; 6.Y.239.239;
25 6.Y.239.154; 6.Y.239.157; 6.Y.239.166; 6.Y.239.169; 6.Y.239.172; 6.Y.239.175;
6.Y.239.240; 6.Y.239.244; 6.Y.154.228; 6.Y.154.229; 6.Y.154.230; 6.Y.154.231;
6.Y.154.236; 6.Y.154.237; 6.Y.154.238; 6.Y.154.239; 6.Y.154.154; 6.Y.154.157;
6.Y.154.166; 6.Y.154.169; 6.Y.154.172; 6.Y.154.175; 6.Y.154.240; 6.Y.154.244;
6.Y.157.228; 6.Y.157.229; 6.Y.157.230; 6.Y.157.231; 6.Y.157.236; 6.Y.157.237;
30 6.Y.157.238; 6.Y.157.239; 6.Y.157.154; 6.Y.157.157; 6.Y.157.166; 6.Y.157.169;
6.Y.157.172; 6.Y.157.175; 6.Y.157.240; 6.Y.157.244; 6.Y.166.228; 6.Y.166.229;
6.Y.166.230; 6.Y.166.231; 6.Y.166.236; 6.Y.166.237; 6.Y.166.238; 6.Y.166.239;
6.Y.166.154; 6.Y.166.157; 6.Y.166.166; 6.Y.166.169; 6.Y.166.172; 6.Y.166.175;
6.Y.166.240; 6.Y.166.244; 6.Y.169.228; 6.Y.169.229; 6.Y.169.230; 6.Y.169.231;
35 6.Y.169.236; 6.Y.169.237; 6.Y.169.238; 6.Y.169.239; 6.Y.169.154; 6.Y.169.157;
6.Y.169.166; 6.Y.169.169; 6.Y.169.172; 6.Y.169.175; 6.Y.169.240; 6.Y.169.244;
6.Y.172.228; 6.Y.172.229; 6.Y.172.230; 6.Y.172.231; 6.Y.172.236; 6.Y.172.237;
6.Y.172.238; 6.Y.172.239; 6.Y.172.154; 6.Y.172.157; 6.Y.172.166; 6.Y.172.169;
6.Y.172.172; 6.Y.172.175; 6.Y.172.240; 6.Y.172.244; 6.Y.175.228; 6.Y.175.229;
40 6.Y.175.230; 6.Y.175.231; 6.Y.175.236; 6.Y.175.237; 6.Y.175.238; 6.Y.175.239;
6.Y.175.154; 6.Y.175.157; 6.Y.175.166; 6.Y.175.169; 6.Y.175.172; 6.Y.175.175;
6.Y.175.240; 6.Y.175.244; 6.Y.240.228; 6.Y.240.229; 6.Y.240.230; 6.Y.240.231;
6.Y.240.236; 6.Y.240.237; 6.Y.240.238; 6.Y.240.239; 6.Y.240.154; 6.Y.240.157;
6.Y.240.166; 6.Y.240.169; 6.Y.240.172; 6.Y.240.175; 6.Y.240.240; 6.Y.240.244;
45 6.Y.244.228; 6.Y.244.229; 6.Y.244.230; 6.Y.244.231; 6.Y.244.236; 6.Y.244.237;
6.Y.244.238; 6.Y.244.239; 6.Y.244.154; 6.Y.244.157; 6.Y.244.166; 6.Y.244.169;
6.Y.244.172; 6.Y.244.175; 6.Y.244.240; 6.Y.244.244;

Prodrugs of 7.AH

- 7.AH.4.157; 7.AH.4.158; 7.AH.4.196; 7.AH.4.223; 7.AH.4.240; 7.AH.4.244; 7.AH.4.243;
 7.AH.4.247; 7.AH.5.157; 7.AH.5.158; 7.AH.5.196; 7.AH.5.223; 7.AH.5.240; 7.AH.5.244;
 7.AH.5.243; 7.AH.5.247; 7.AH.7.157; 7.AH.7.158; 7.AH.7.196; 7.AH.7.223; 7.AH.7.240;
 5 7.AH.7.244; 7.AH.7.243; 7.AH.7.247; 7.AH.15.157; 7.AH.15.158; 7.AH.15.196;
 7.AH.15.223; 7.AH.15.240; 7.AH.15.244; 7.AH.15.243; 7.AH.15.247; 7.AH.16.157;
 7.AH.16.158; 7.AH.16.196; 7.AH.16.223; 7.AH.16.240; 7.AH.16.244; 7.AH.16.243;
 7.AH.16.247; 7.AH.18.157; 7.AH.18.158; 7.AH.18.196; 7.AH.18.223; 7.AH.18.240;
 7.AH.18.244; 7.AH.18.243; 7.AH.18.247; 7.AH.26.157; 7.AH.26.158; 7.AH.26.196;
 10 7.AH.26.223; 7.AH.26.240; 7.AH.26.244; 7.AH.26.243; 7.AH.26.247; 7.AH.27.157;
 7.AH.27.158; 7.AH.27.196; 7.AH.27.223; 7.AH.27.240; 7.AH.27.244; 7.AH.27.243;
 7.AH.27.247; 7.AH.29.157; 7.AH.29.158; 7.AH.29.196; 7.AH.29.223; 7.AH.29.240;
 7.AH.29.244; 7.AH.29.243; 7.AH.29.247; 7.AH.54.157; 7.AH.54.158; 7.AH.54.196;
 7.AH.54.223; 7.AH.54.240; 7.AH.54.244; 7.AH.54.243; 7.AH.54.247; 7.AH.55.157;
 15 7.AH.55.158; 7.AH.55.196; 7.AH.55.223; 7.AH.55.240; 7.AH.55.244; 7.AH.55.243;
 7.AH.55.247; 7.AH.56.157; 7.AH.56.158; 7.AH.56.196; 7.AH.56.223; 7.AH.56.240;
 7.AH.56.244; 7.AH.56.243; 7.AH.56.247; 7.AH.157.157; 7.AH.157.158; 7.AH.157.196;
 7.AH.157.223; 7.AH.157.240; 7.AH.157.244; 7.AH.157.243; 7.AH.157.247; 7.AH.196.157;
 7.AH.196.158; 7.AH.196.196; 7.AH.196.223; 7.AH.196.240; 7.AH.196.244; 7.AH.196.243;
 20 7.AH.196.247; 7.AH.223.157; 7.AH.223.158; 7.AH.223.196; 7.AH.223.223; 7.AH.223.240;
 7.AH.223.244; 7.AH.223.243; 7.AH.223.247; 7.AH.240.157; 7.AH.240.158; 7.AH.240.196;
 7.AH.240.223; 7.AH.240.240; 7.AH.240.244; 7.AH.240.243; 7.AH.240.247; 7.AH.244.157;
 7.AH.244.158; 7.AH.244.196; 7.AH.244.223; 7.AH.244.240; 7.AH.244.244; 7.AH.244.243;
 7.AH.244.247; 7.AH.247.157; 7.AH.247.158; 7.AH.247.196; 7.AH.247.223; 7.AH.247.240;
 25 7.AH.247.244; 7.AH.247.243; 7.AH.247.247;

Prodrugs of 7.AI

- 7.AI.4.157; 7.AI.4.158; 7.AI.4.196; 7.AI.4.223; 7.AI.4.240; 7.AI.4.244; 7.AI.4.243;
 7.AI.4.247; 7.AI.5.157; 7.AI.5.158; 7.AI.5.196; 7.AI.5.223; 7.AI.5.240; 7.AI.5.244;
 30 7.AI.5.243; 7.AI.5.247; 7.AI.7.157; 7.AI.7.158; 7.AI.7.196; 7.AI.7.223; 7.AI.7.240;
 7.AI.7.244; 7.AI.7.243; 7.AI.7.247; 7.AI.15.157; 7.AI.15.158; 7.AI.15.196; 7.AI.15.223;
 7.AI.15.240; 7.AI.15.244; 7.AI.15.243; 7.AI.15.247; 7.AI.16.157; 7.AI.16.158; 7.AI.16.196;
 7.AI.16.223; 7.AI.16.240; 7.AI.16.244; 7.AI.16.243; 7.AI.16.247; 7.AI.18.157; 7.AI.18.158;
 7.AI.18.196; 7.AI.18.223; 7.AI.18.240; 7.AI.18.244; 7.AI.18.243; 7.AI.18.247; 7.AI.26.157;
 35 7.AI.26.158; 7.AI.26.196; 7.AI.26.223; 7.AI.26.240; 7.AI.26.244; 7.AI.26.243; 7.AI.26.247;
 7.AI.27.157; 7.AI.27.158; 7.AI.27.196; 7.AI.27.223; 7.AI.27.240; 7.AI.27.244; 7.AI.27.243;
 7.AI.27.247; 7.AI.29.157; 7.AI.29.158; 7.AI.29.196; 7.AI.29.223; 7.AI.29.240; 7.AI.29.244;
 7.AI.29.243; 7.AI.29.247; 7.AI.54.157; 7.AI.54.158; 7.AI.54.196; 7.AI.54.223; 7.AI.54.240;
 7.AI.54.244; 7.AI.54.243; 7.AI.54.247; 7.AI.55.157; 7.AI.55.158; 7.AI.55.196; 7.AI.55.223;
 40 7.AI.55.240; 7.AI.55.244; 7.AI.55.243; 7.AI.55.247; 7.AI.56.157; 7.AI.56.158; 7.AI.56.196;
 7.AI.56.223; 7.AI.56.240; 7.AI.56.244; 7.AI.56.243; 7.AI.56.247; 7.AI.157.157;
 7.AI.157.158; 7.AI.157.196; 7.AI.157.223; 7.AI.157.240; 7.AI.157.244; 7.AI.157.243;
 7.AI.157.247; 7.AI.196.157; 7.AI.196.158; 7.AI.196.196; 7.AI.196.223; 7.AI.196.240;
 7.AI.196.244; 7.AI.196.243; 7.AI.196.247; 7.AI.223.157; 7.AI.223.158; 7.AI.223.196;
 45 7.AI.223.223; 7.AI.223.240; 7.AI.223.244; 7.AI.223.243; 7.AI.223.247; 7.AI.240.157;
 7.AI.240.158; 7.AI.240.196; 7.AI.240.223; 7.AI.240.240; 7.AI.240.244; 7.AI.240.243;
 7.AI.240.247; 7.AI.244.157; 7.AI.244.158; 7.AI.244.196; 7.AI.244.223; 7.AI.244.240;

7.AJ.244.244; 7.AJ.244.243; 7.AJ.244.247; 7.AJ.247.157; 7.AJ.247.158; 7.AJ.247.196;
7.AJ.247.223; 7.AJ.247.240; 7.AJ.247.244; 7.AJ.247.243; 7.AJ.247.247;

Prodrugs of 7.AN

- 5 7.AN.4.157; 7.AN.4.158; 7.AN.4.196; 7.AN.4.223; 7.AN.4.240; 7.AN.4.244; 7.AN.4.243;
7.AN.4.247; 7.AN.5.157; 7.AN.5.158; 7.AN.5.196; 7.AN.5.223; 7.AN.5.240; 7.AN.5.244;
7.AN.5.243; 7.AN.5.247; 7.AN.7.157; 7.AN.7.158; 7.AN.7.196; 7.AN.7.223; 7.AN.7.240;
7.AN.7.244; 7.AN.7.243; 7.AN.7.247; 7.AN.15.157; 7.AN.15.158; 7.AN.15.196;
7.AN.15.223; 7.AN.15.240; 7.AN.15.244; 7.AN.15.243; 7.AN.15.247; 7.AN.16.157;
10 7.AN.16.158; 7.AN.16.196; 7.AN.16.223; 7.AN.16.240; 7.AN.16.244; 7.AN.16.243;
7.AN.16.247; 7.AN.18.157; 7.AN.18.158; 7.AN.18.196; 7.AN.18.223; 7.AN.18.240;
7.AN.18.244; 7.AN.18.243; 7.AN.18.247; 7.AN.26.157; 7.AN.26.158; 7.AN.26.196;
7.AN.26.223; 7.AN.26.240; 7.AN.26.244; 7.AN.26.243; 7.AN.26.247; 7.AN.27.157;
7.AN.27.158; 7.AN.27.196; 7.AN.27.223; 7.AN.27.240; 7.AN.27.244; 7.AN.27.243;
15 7.AN.27.247; 7.AN.29.157; 7.AN.29.158; 7.AN.29.196; 7.AN.29.223; 7.AN.29.240;
7.AN.29.244; 7.AN.29.243; 7.AN.29.247; 7.AN.54.157; 7.AN.54.158; 7.AN.54.196;
7.AN.54.223; 7.AN.54.240; 7.AN.54.244; 7.AN.54.243; 7.AN.54.247; 7.AN.55.157;
7.AN.55.158; 7.AN.55.196; 7.AN.55.223; 7.AN.55.240; 7.AN.55.244; 7.AN.55.243;
7.AN.55.247; 7.AN.56.157; 7.AN.56.158; 7.AN.56.196; 7.AN.56.223; 7.AN.56.240;
20 7.AN.56.244; 7.AN.56.243; 7.AN.56.247; 7.AN.157.157; 7.AN.157.158; 7.AN.157.196;
7.AN.157.223; 7.AN.157.240; 7.AN.157.244; 7.AN.157.243; 7.AN.157.247; 7.AN.196.157;
7.AN.196.158; 7.AN.196.196; 7.AN.196.223; 7.AN.196.240; 7.AN.196.244; 7.AN.196.243;
7.AN.196.247; 7.AN.223.157; 7.AN.223.158; 7.AN.223.196; 7.AN.223.223; 7.AN.223.240;
7.AN.223.244; 7.AN.223.243; 7.AN.223.247; 7.AN.240.157; 7.AN.240.158; 7.AN.240.196;
25 7.AN.240.223; 7.AN.240.240; 7.AN.240.244; 7.AN.240.243; 7.AN.240.247; 7.AN.244.157;
7.AN.244.158; 7.AN.244.196; 7.AN.244.223; 7.AN.244.240; 7.AN.244.244; 7.AN.244.243;
7.AN.244.247; 7.AN.247.157; 7.AN.247.158; 7.AN.247.196; 7.AN.247.223; 7.AN.247.240;
7.AN.247.244; 7.AN.247.243; 7.AN.247.247;

30 Prodrugs of 7.AP

- 7.AP.4.157; 7.AP.4.158; 7.AP.4.196; 7.AP.4.223; 7.AP.4.240; 7.AP.4.244; 7.AP.4.243;
7.AP.4.247; 7.AP.5.157; 7.AP.5.158; 7.AP.5.196; 7.AP.5.223; 7.AP.5.240; 7.AP.5.244;
7.AP.5.243; 7.AP.5.247; 7.AP.7.157; 7.AP.7.158; 7.AP.7.196; 7.AP.7.223; 7.AP.7.240;
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Prodrugs of 7.AZ

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Prodrugs of 7.BF

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Prodrugs of 7.CI

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Prodrugs of 7.CO

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Prodrugs of 8.AH

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40 Prodrugs of 8.AJ

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 10 8.AJ.223.223; 8.AJ.223.240; 8.AJ.223.244; 8.AJ.223.243; 8.AJ.223.247; 8.AJ.240.157;
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 8.AJ.247.223; 8.AJ.247.240; 8.AJ.247.244; 8.AJ.247.243; 8.AJ.247.247;

15

Prodrugs of 8.AN

8.AN.4.157; 8.AN.4.158; 8.AN.4.196; 8.AN.4.223; 8.AN.4.240; 8.AN.4.244; 8.AN.4.243;
 8.AN.4.247; 8.AN.5.157; 8.AN.5.158; 8.AN.5.196; 8.AN.5.223; 8.AN.5.240; 8.AN.5.244;
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 8.AN.15.223; 8.AN.15.240; 8.AN.15.244; 8.AN.15.243; 8.AN.15.247; 8.AN.16.157;
 8.AN.16.158; 8.AN.16.196; 8.AN.16.223; 8.AN.16.240; 8.AN.16.244; 8.AN.16.243;
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 8.AN.18.244; 8.AN.18.243; 8.AN.18.247; 8.AN.26.157; 8.AN.26.158; 8.AN.26.196;
 25 8.AN.26.223; 8.AN.26.240; 8.AN.26.244; 8.AN.26.243; 8.AN.26.247; 8.AN.27.157;
 8.AN.27.158; 8.AN.27.196; 8.AN.27.223; 8.AN.27.240; 8.AN.27.244; 8.AN.27.243;
 8.AN.27.247; 8.AN.29.157; 8.AN.29.158; 8.AN.29.196; 8.AN.29.223; 8.AN.29.240;
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 35 8.AN.196.247; 8.AN.223.157; 8.AN.223.158; 8.AN.223.196; 8.AN.223.223; 8.AN.223.240;
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 40 8.AN.247.244; 8.AN.247.243; 8.AN.247.247;

Prodrugs of 8.AP

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 8.AP.4.247; 8.AP.5.157; 8.AP.5.158; 8.AP.5.196; 8.AP.5.223; 8.AP.5.240; 8.AP.5.244;
 45 8.AP.5.243; 8.AP.5.247; 8.AP.7.157; 8.AP.7.158; 8.AP.7.196; 8.AP.7.223; 8.AP.7.240;
 8.AP.7.244; 8.AP.7.243; 8.AP.7.247; 8.AP.15.157; 8.AP.15.158; 8.AP.15.196; 8.AP.15.223;
 8.AP.15.240; 8.AP.15.244; 8.AP.15.243; 8.AP.15.247; 8.AP.16.157; 8.AP.16.158;
 8.AP.16.196; 8.AP.16.223; 8.AP.16.240; 8.AP.16.244; 8.AP.16.243; 8.AP.16.247;

- 8.AP.18.157; 8.AP.18.158; 8.AP.18.196; 8.AP.18.223; 8.AP.18.240; 8.AP.18.244;
 8.AP.18.243; 8.AP.18.247; 8.AP.26.157; 8.AP.26.158; 8.AP.26.196; 8.AP.26.223;
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 10 8.AP.56.243; 8.AP.56.247; 8.AP.157.157; 8.AP.157.158; 8.AP.157.196; 8.AP.157.223;
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 15 8.AP.240.240; 8.AP.240.244; 8.AP.240.243; 8.AP.240.247; 8.AP.244.157; 8.AP.244.158;
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 8.AP.247.243; 8.AP.247.247;
- 20 Prodrugs of 8.AZ
 8.AZ.4.157; 8.AZ.4.158; 8.AZ.4.196; 8.AZ.4.223; 8.AZ.4.240; 8.AZ.4.244; 8.AZ.4.243;
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 8.AZ.7.244; 8.AZ.7.243; 8.AZ.7.247; 8.AZ.15.157; 8.AZ.15.158; 8.AZ.15.196; 8.AZ.15.223;
 25 8.AZ.15.240; 8.AZ.15.244; 8.AZ.15.243; 8.AZ.15.247; 8.AZ.16.157; 8.AZ.16.158;
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 8.AZ.18.157; 8.AZ.18.158; 8.AZ.18.196; 8.AZ.18.223; 8.AZ.18.240; 8.AZ.18.244;
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 8.AZ.55.196; 8.AZ.55.223; 8.AZ.55.240; 8.AZ.55.244; 8.AZ.55.243; 8.AZ.55.247;
 35 8.AZ.56.157; 8.AZ.56.158; 8.AZ.56.196; 8.AZ.56.223; 8.AZ.56.240; 8.AZ.56.244;
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 40 8.AZ.223.243; 8.AZ.223.247; 8.AZ.240.157; 8.AZ.240.158; 8.AZ.240.196; 8.AZ.240.223;
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 8.AZ.247.243; 8.AZ.247.247;
- 45 Prodrugs of 8.BF
 8.BF.4.157; 8.BF.4.158; 8.BF.4.196; 8.BF.4.223; 8.BF.4.240; 8.BF.4.244; 8.BF.4.243;
 8.BF.4.247; 8.BF.5.157; 8.BF.5.158; 8.BF.5.196; 8.BF.5.223; 8.BF.5.240; 8.BF.5.244;

- 8.BF.5.243; 8.BF.5.247; 8.BF.7.157; 8.BF.7.158; 8.BF.7.196; 8.BF.7.223; 8.BF.7.240;
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 8.BF.15.240; 8.BF.15.244; 8.BF.15.243; 8.BF.15.247; 8.BF.16.157; 8.BF.16.158;
 8.BF.16.196; 8.BF.16.223; 8.BF.16.240; 8.BF.16.244; 8.BF.16.243; 8.BF.16.247;
 5 8.BF.18.157; 8.BF.18.158; 8.BF.18.196; 8.BF.18.223; 8.BF.18.240; 8.BF.18.244;
 8.BF.18.243; 8.BF.18.247; 8.BF.26.157; 8.BF.26.158; 8.BF.26.196; 8.BF.26.223;
 8.BF.26.240; 8.BF.26.244; 8.BF.26.243; 8.BF.26.247; 8.BF.27.157; 8.BF.27.158;
 8.BF.27.196; 8.BF.27.223; 8.BF.27.240; 8.BF.27.244; 8.BF.27.243; 8.BF.27.247;
 8.BF.29.157; 8.BF.29.158; 8.BF.29.196; 8.BF.29.223; 8.BF.29.240; 8.BF.29.244;
 10 8.BF.29.243; 8.BF.29.247; 8.BF.54.157; 8.BF.54.158; 8.BF.54.196; 8.BF.54.223;
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 15 8.BF.157.240; 8.BF.157.244; 8.BF.157.243; 8.BF.157.247; 8.BF.196.157; 8.BF.196.158;
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 20 8.BF.244.196; 8.BF.244.223; 8.BF.244.240; 8.BF.244.244; 8.BF.244.243; 8.BF.244.247;
 8.BF.247.157; 8.BF.247.158; 8.BF.247.196; 8.BF.247.223; 8.BF.247.240; 8.BF.247.244;
 8.BF.247.243; 8.BF.247.247;

Prodrugs of 8.CI

- 25 8.CI.4.157; 8.CI.4.158; 8.CI.4.196; 8.CI.4.223; 8.CI.4.240; 8.CI.4.244; 8.CI.4.243;
 8.CI.4.247; 8.CI.5.157; 8.CI.5.158; 8.CI.5.196; 8.CI.5.223; 8.CI.5.240; 8.CI.5.244;
 8.CI.5.243; 8.CI.5.247; 8.CI.7.157; 8.CI.7.158; 8.CI.7.196; 8.CI.7.223; 8.CI.7.240;
 8.CI.7.244; 8.CI.7.243; 8.CI.7.247; 8.CI.15.157; 8.CI.15.158; 8.CI.15.196; 8.CI.15.223;
 8.CI.15.240; 8.CI.15.244; 8.CI.15.243; 8.CI.15.247; 8.CI.16.157; 8.CI.16.158; 8.CI.16.196;
 30 8.CI.16.223; 8.CI.16.240; 8.CI.16.244; 8.CI.16.243; 8.CI.16.247; 8.CI.18.157; 8.CI.18.158;
 8.CI.18.196; 8.CI.18.223; 8.CI.18.240; 8.CI.18.244; 8.CI.18.243; 8.CI.18.247; 8.CI.26.157;
 8.CI.26.158; 8.CI.26.196; 8.CI.26.223; 8.CI.26.240; 8.CI.26.244; 8.CI.26.243; 8.CI.26.247;
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 8.CI.27.247; 8.CI.29.157; 8.CI.29.158; 8.CI.29.196; 8.CI.29.223; 8.CI.29.240; 8.CI.29.244;
 35 8.CI.29.243; 8.CI.29.247; 8.CI.54.157; 8.CI.54.158; 8.CI.54.196; 8.CI.54.223; 8.CI.54.240;
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Prodrugs of 8.CO

- 8.CO.4.157; 8.CO.4.158; 8.CO.4.196; 8.CO.4.223; 8.CO.4.240; 8.CO.4.244; 8.CO.4.243;
 8.CO.4.247; 8.CO.5.157; 8.CO.5.158; 8.CO.5.196; 8.CO.5.223; 8.CO.5.240; 8.CO.5.244;
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 8.CO.7.244; 8.CO.7.243; 8.CO.7.247; 8.CO.15.157; 8.CO.15.158; 8.CO.15.196;
 5 8.CO.15.223; 8.CO.15.240; 8.CO.15.244; 8.CO.15.243; 8.CO.15.247; 8.CO.16.157;
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 8.CO.26.223; 8.CO.26.240; 8.CO.26.244; 8.CO.26.243; 8.CO.26.247; 8.CO.27.157;
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 8.CO.247.244; 8.CO.247.243; 8.CO.247.247;

25

Prodrugs of 9.AH

- 9.AH.4.157; 9.AH.4.158; 9.AH.4.196; 9.AH.4.223; 9.AH.4.240; 9.AH.4.244; 9.AH.4.243;
 9.AH.4.247; 9.AH.5.157; 9.AH.5.158; 9.AH.5.196; 9.AH.5.223; 9.AH.5.240; 9.AH.5.244;
 9.AH.5.243; 9.AH.5.247; 9.AH.7.157; 9.AH.7.158; 9.AH.7.196; 9.AH.7.223; 9.AH.7.240;
 30 9.AH.7.244; 9.AH.7.243; 9.AH.7.247; 9.AH.15.157; 9.AH.15.158; 9.AH.15.196;
 9.AH.15.223; 9.AH.15.240; 9.AH.15.244; 9.AH.15.243; 9.AH.15.247; 9.AH.16.157;
 9.AH.16.158; 9.AH.16.196; 9.AH.16.223; 9.AH.16.240; 9.AH.16.244; 9.AH.16.243;
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Prodrugs of 9.AI

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Prodrugs of 9.AN

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Prodrugs of 9.AP

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Prodrugs of 9.AZ

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10 Prodrugs of 9.BF

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Prodrugs of 9.CI

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Prodrugs of 9.CO

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Prodrugs of 10.AZ

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Prodrugs of 12.AP

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Prodrugs of 12.AZ

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Prodrugs of 12.BF

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Prodrugs of 12.Cl

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Prodrugs of 12.CO

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30 12.CO.247.244; 12.CO.247.243; 12.CO.247.247.

Prodrugs of 13.B

- 13.B.228.228; 13.B.228.229; 13.B.228.230; 13.B.228.231; 13.B.228.236; 13.B.228.237;
 13.B.228.238; 13.B.228.239; 13.B.228.154; 13.B.228.157; 13.B.228.166; 13.B.228.169;
 5 13.B.228.172; 13.B.228.175; 13.B.228.240; 13.B.228.244; 13.B.229.228; 13.B.229.229;
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 13.B.175.154; 13.B.175.157; 13.B.175.166; 13.B.175.169; 13.B.175.172; 13.B.175.175;
 40 13.B.175.240; 13.B.175.244; 13.B.240.228; 13.B.240.229; 13.B.240.230; 13.B.240.231;
 13.B.240.236; 13.B.240.237; 13.B.240.238; 13.B.240.239; 13.B.240.154; 13.B.240.157;
 13.B.240.166; 13.B.240.169; 13.B.240.172; 13.B.240.175; 13.B.240.240; 13.B.240.244;
 13.B.244.228; 13.B.244.229; 13.B.244.230; 13.B.244.231; 13.B.244.236; 13.B.244.237;
 13.B.244.238; 13.B.244.239; 13.B.244.154; 13.B.244.157; 13.B.244.166; 13.B.244.169;
 45 13.B.244.172; 13.B.244.175; 13.B.244.240; 13.B.244.244;

Prodrugs of 13.D

13.D.228.228; 13.D.228.229; 13.D.228.230; 13.D.228.231; 13.D.228.236; 13.D.228.237;
13.D.228.238; 13.D.228.239; 13.D.228.154; 13.D.228.157; 13.D.228.166; 13.D.228.169;
13.D.228.172; 13.D.228.175; 13.D.228.240; 13.D.228.244; 13.D.229.228; 13.D.229.229;
5 13.D.229.230; 13.D.229.231; 13.D.229.236; 13.D.229.237; 13.D.229.238; 13.D.229.239;
13.D.229.154; 13.D.229.157; 13.D.229.166; 13.D.229.169; 13.D.229.172; 13.D.229.175;
13.D.229.240; 13.D.229.244; 13.D.230.228; 13.D.230.229; 13.D.230.230; 13.D.230.231;
13.D.230.236; 13.D.230.237; 13.D.230.238; 13.D.230.239; 13.D.230.154; 13.D.230.157;
13.D.230.166; 13.D.230.169; 13.D.230.172; 13.D.230.175; 13.D.230.240; 13.D.230.244;
10 13.D.231.228; 13.D.231.229; 13.D.231.230; 13.D.231.231; 13.D.231.236; 13.D.231.237;
13.D.231.238; 13.D.231.239; 13.D.231.154; 13.D.231.157; 13.D.231.166; 13.D.231.169;
13.D.231.172; 13.D.231.175; 13.D.231.240; 13.D.231.244; 13.D.236.228; 13.D.236.229;
13.D.236.230; 13.D.236.231; 13.D.236.236; 13.D.236.237; 13.D.236.238; 13.D.236.239;
13.D.236.154; 13.D.236.157; 13.D.236.166; 13.D.236.169; 13.D.236.172; 13.D.236.175;
15 13.D.236.240; 13.D.236.244; 13.D.237.228; 13.D.237.229; 13.D.237.230; 13.D.237.231;
13.D.237.236; 13.D.237.237; 13.D.237.238; 13.D.237.239; 13.D.237.154; 13.D.237.157;
13.D.237.166; 13.D.237.169; 13.D.237.172; 13.D.237.175; 13.D.237.240; 13.D.237.244;
13.D.238.228; 13.D.238.229; 13.D.238.230; 13.D.238.231; 13.D.238.236; 13.D.238.237;
13.D.238.238; 13.D.238.239; 13.D.238.154; 13.D.238.157; 13.D.238.166; 13.D.238.169;
20 13.D.238.172; 13.D.238.175; 13.D.238.240; 13.D.238.244; 13.D.239.228; 13.D.239.229;
13.D.239.230; 13.D.239.231; 13.D.239.236; 13.D.239.237; 13.D.239.238; 13.D.239.239;
13.D.239.154; 13.D.239.157; 13.D.239.166; 13.D.239.169; 13.D.239.172; 13.D.239.175;
13.D.239.240; 13.D.239.244; 13.D.154.228; 13.D.154.229; 13.D.154.230; 13.D.154.231;
13.D.154.236; 13.D.154.237; 13.D.154.238; 13.D.154.239; 13.D.154.154; 13.D.154.157;
25 13.D.154.166; 13.D.154.169; 13.D.154.172; 13.D.154.175; 13.D.154.240; 13.D.154.244;
13.D.157.228; 13.D.157.229; 13.D.157.230; 13.D.157.231; 13.D.157.236; 13.D.157.237;
13.D.157.238; 13.D.157.239; 13.D.157.154; 13.D.157.157; 13.D.157.166; 13.D.157.169;
13.D.157.172; 13.D.157.175; 13.D.157.240; 13.D.157.244; 13.D.166.228; 13.D.166.229;
13.D.166.230; 13.D.166.231; 13.D.166.236; 13.D.166.237; 13.D.166.238; 13.D.166.239;
30 13.D.166.154; 13.D.166.157; 13.D.166.166; 13.D.166.169; 13.D.166.172; 13.D.166.175;
13.D.166.240; 13.D.166.244; 13.D.169.228; 13.D.169.229; 13.D.169.230; 13.D.169.231;
13.D.169.236; 13.D.169.237; 13.D.169.238; 13.D.169.239; 13.D.169.154; 13.D.169.157;
13.D.169.166; 13.D.169.169; 13.D.169.172; 13.D.169.175; 13.D.169.240; 13.D.169.244;
13.D.172.228; 13.D.172.229; 13.D.172.230; 13.D.172.231; 13.D.172.236; 13.D.172.237;
35 13.D.172.238; 13.D.172.239; 13.D.172.154; 13.D.172.157; 13.D.172.166; 13.D.172.169;
13.D.172.172; 13.D.172.175; 13.D.172.240; 13.D.172.244; 13.D.175.228; 13.D.175.229;
13.D.175.230; 13.D.175.231; 13.D.175.236; 13.D.175.237; 13.D.175.238; 13.D.175.239;
13.D.175.154; 13.D.175.157; 13.D.175.166; 13.D.175.169; 13.D.175.172; 13.D.175.175;
13.D.175.240; 13.D.175.244; 13.D.240.228; 13.D.240.229; 13.D.240.230; 13.D.240.231;
40 13.D.240.236; 13.D.240.237; 13.D.240.238; 13.D.240.239; 13.D.240.154; 13.D.240.157;
13.D.240.166; 13.D.240.169; 13.D.240.172; 13.D.240.175; 13.D.240.240; 13.D.240.244;
13.D.244.228; 13.D.244.229; 13.D.244.230; 13.D.244.231; 13.D.244.236; 13.D.244.237;
13.D.244.238; 13.D.244.239; 13.D.244.154; 13.D.244.157; 13.D.244.166; 13.D.244.169;
13.D.244.172; 13.D.244.175; 13.D.244.240; 13.D.244.244;

45

Prodrugs of 13.E

13.E.228.228; 13.E.228.229; 13.E.228.230; 13.E.228.231; 13.E.228.236; 13.E.228.237;
13.E.228.238; 13.E.228.239; 13.E.228.154; 13.E.228.157; 13.E.228.166; 13.E.228.169;
13.E.228.172; 13.E.228.175; 13.E.228.240; 13.E.228.244; 13.E.229.228; 13.E.229.229;
13.E.229.230; 13.E.229.231; 13.E.229.236; 13.E.229.237; 13.E.229.238; 13.E.229.239;
5 13.E.229.154; 13.E.229.157; 13.E.229.166; 13.E.229.169; 13.E.229.172; 13.E.229.175;
13.E.229.240; 13.E.229.244; 13.E.230.228; 13.E.230.229; 13.E.230.230; 13.E.230.231;
13.E.230.236; 13.E.230.237; 13.E.230.238; 13.E.230.239; 13.E.230.154; 13.E.230.157;
13.E.230.166; 13.E.230.169; 13.E.230.172; 13.E.230.175; 13.E.230.240; 13.E.230.244;
13.E.231.228; 13.E.231.229; 13.E.231.230; 13.E.231.231; 13.E.231.236; 13.E.231.237;
10 13.E.231.238; 13.E.231.239; 13.E.231.154; 13.E.231.157; 13.E.231.166; 13.E.231.169;
13.E.231.172; 13.E.231.175; 13.E.231.240; 13.E.231.244; 13.E.236.228; 13.E.236.229;
13.E.236.230; 13.E.236.231; 13.E.236.236; 13.E.236.237; 13.E.236.238; 13.E.236.239;
13.E.236.154; 13.E.236.157; 13.E.236.166; 13.E.236.169; 13.E.236.172; 13.E.236.175;
13.E.236.240; 13.E.236.244; 13.E.237.228; 13.E.237.229; 13.E.237.230; 13.E.237.231;
15 13.E.237.236; 13.E.237.237; 13.E.237.238; 13.E.237.239; 13.E.237.154; 13.E.237.157;
13.E.237.166; 13.E.237.169; 13.E.237.172; 13.E.237.175; 13.E.237.240; 13.E.237.244;
13.E.238.228; 13.E.238.229; 13.E.238.230; 13.E.238.231; 13.E.238.236; 13.E.238.237;
13.E.238.238; 13.E.238.239; 13.E.238.154; 13.E.238.157; 13.E.238.166; 13.E.238.169;
13.E.238.172; 13.E.238.175; 13.E.238.240; 13.E.238.244; 13.E.239.228; 13.E.239.229;
20 13.E.239.230; 13.E.239.231; 13.E.239.236; 13.E.239.237; 13.E.239.238; 13.E.239.239;
13.E.239.154; 13.E.239.157; 13.E.239.166; 13.E.239.169; 13.E.239.172; 13.E.239.175;
13.E.239.240; 13.E.239.244; 13.E.154.228; 13.E.154.229; 13.E.154.230; 13.E.154.231;
13.E.154.236; 13.E.154.237; 13.E.154.238; 13.E.154.239; 13.E.154.154; 13.E.154.157;
13.E.154.166; 13.E.154.169; 13.E.154.172; 13.E.154.175; 13.E.154.240; 13.E.154.244;
25 13.E.157.228; 13.E.157.229; 13.E.157.230; 13.E.157.231; 13.E.157.236; 13.E.157.237;
13.E.157.238; 13.E.157.239; 13.E.157.154; 13.E.157.157; 13.E.157.166; 13.E.157.169;
13.E.157.172; 13.E.157.175; 13.E.157.240; 13.E.157.244; 13.E.166.228; 13.E.166.229;
13.E.166.230; 13.E.166.231; 13.E.166.236; 13.E.166.237; 13.E.166.238; 13.E.166.239;
13.E.166.154; 13.E.166.157; 13.E.166.166; 13.E.166.169; 13.E.166.172; 13.E.166.175;
30 13.E.166.240; 13.E.166.244; 13.E.169.228; 13.E.169.229; 13.E.169.230; 13.E.169.231;
13.E.169.236; 13.E.169.237; 13.E.169.238; 13.E.169.239; 13.E.169.154; 13.E.169.157;
13.E.169.166; 13.E.169.169; 13.E.169.172; 13.E.169.175; 13.E.169.240; 13.E.169.244;
13.E.172.228; 13.E.172.229; 13.E.172.230; 13.E.172.231; 13.E.172.236; 13.E.172.237;
13.E.172.238; 13.E.172.239; 13.E.172.154; 13.E.172.157; 13.E.172.166; 13.E.172.169;
35 13.E.172.172; 13.E.172.175; 13.E.172.240; 13.E.172.244; 13.E.175.228; 13.E.175.229;
13.E.175.230; 13.E.175.231; 13.E.175.236; 13.E.175.237; 13.E.175.238; 13.E.175.239;
13.E.175.154; 13.E.175.157; 13.E.175.166; 13.E.175.169; 13.E.175.172; 13.E.175.175;
13.E.175.240; 13.E.175.244; 13.E.240.228; 13.E.240.229; 13.E.240.230; 13.E.240.231;
13.E.240.236; 13.E.240.237; 13.E.240.238; 13.E.240.239; 13.E.240.154; 13.E.240.157;
40 13.E.240.166; 13.E.240.169; 13.E.240.172; 13.E.240.175; 13.E.240.240; 13.E.240.244;
13.E.244.228; 13.E.244.229; 13.E.244.230; 13.E.244.231; 13.E.244.236; 13.E.244.237;
13.E.244.238; 13.E.244.239; 13.E.244.154; 13.E.244.157; 13.E.244.166; 13.E.244.169;
13.E.244.172; 13.E.244.175; 13.E.244.240; 13.E.244.244;

45 Prodrugs of 13.G

13.G.228.228; 13.G.228.229; 13.G.228.230; 13.G.228.231; 13.G.228.236; 13.G.228.237;
13.G.228.238; 13.G.228.239; 13.G.228.154; 13.G.228.157; 13.G.228.166; 13.G.228.169;
13.G.228.172; 13.G.228.175; 13.G.228.240; 13.G.228.244; 13.G.229.228; 13.G.229.229;
13.G.229.230; 13.G.229.231; 13.G.229.236; 13.G.229.237; 13.G.229.238; 13.G.229.239;
5 13.G.229.154; 13.G.229.157; 13.G.229.166; 13.G.229.169; 13.G.229.172; 13.G.229.175;
13.G.229.240; 13.G.229.244; 13.G.230.228; 13.G.230.229; 13.G.230.230; 13.G.230.231;
13.G.230.236; 13.G.230.237; 13.G.230.238; 13.G.230.239; 13.G.230.154; 13.G.230.157;
13.G.230.166; 13.G.230.169; 13.G.230.172; 13.G.230.175; 13.G.230.240; 13.G.230.244;
13.G.231.228; 13.G.231.229; 13.G.231.230; 13.G.231.231; 13.G.231.236; 13.G.231.237;
10 13.G.231.238; 13.G.231.239; 13.G.231.154; 13.G.231.157; 13.G.231.166; 13.G.231.169;
13.G.231.172; 13.G.231.175; 13.G.231.240; 13.G.231.244; 13.G.236.228; 13.G.236.229;
13.G.236.230; 13.G.236.231; 13.G.236.236; 13.G.236.237; 13.G.236.238; 13.G.236.239;
13.G.236.154; 13.G.236.157; 13.G.236.166; 13.G.236.169; 13.G.236.172; 13.G.236.175;
13.G.236.240; 13.G.236.244; 13.G.237.228; 13.G.237.229; 13.G.237.230; 13.G.237.231;
15 13.G.237.236; 13.G.237.237; 13.G.237.238; 13.G.237.239; 13.G.237.154; 13.G.237.157;
13.G.237.166; 13.G.237.169; 13.G.237.172; 13.G.237.175; 13.G.237.240; 13.G.237.244;
13.G.238.228; 13.G.238.229; 13.G.238.230; 13.G.238.231; 13.G.238.236; 13.G.238.237;
13.G.238.238; 13.G.238.239; 13.G.238.154; 13.G.238.157; 13.G.238.166; 13.G.238.169;
13.G.238.172; 13.G.238.175; 13.G.238.240; 13.G.238.244; 13.G.239.228; 13.G.239.229;
20 13.G.239.230; 13.G.239.231; 13.G.239.236; 13.G.239.237; 13.G.239.238; 13.G.239.239;
13.G.239.154; 13.G.239.157; 13.G.239.166; 13.G.239.169; 13.G.239.172; 13.G.239.175;
13.G.239.240; 13.G.239.244; 13.G.154.228; 13.G.154.229; 13.G.154.230; 13.G.154.231;
13.G.154.236; 13.G.154.237; 13.G.154.238; 13.G.154.239; 13.G.154.154; 13.G.154.157;
13.G.154.166; 13.G.154.169; 13.G.154.172; 13.G.154.175; 13.G.154.240; 13.G.154.244;
25 13.G.157.228; 13.G.157.229; 13.G.157.230; 13.G.157.231; 13.G.157.236; 13.G.157.237;
13.G.157.238; 13.G.157.239; 13.G.157.154; 13.G.157.157; 13.G.157.166; 13.G.157.169;
13.G.157.172; 13.G.157.175; 13.G.157.240; 13.G.157.244; 13.G.166.228; 13.G.166.229;
13.G.166.230; 13.G.166.231; 13.G.166.236; 13.G.166.237; 13.G.166.238; 13.G.166.239;
13.G.166.154; 13.G.166.157; 13.G.166.166; 13.G.166.169; 13.G.166.172; 13.G.166.175;
30 13.G.166.240; 13.G.166.244; 13.G.169.228; 13.G.169.229; 13.G.169.230; 13.G.169.231;
13.G.169.236; 13.G.169.237; 13.G.169.238; 13.G.169.239; 13.G.169.154; 13.G.169.157;
13.G.169.166; 13.G.169.169; 13.G.169.172; 13.G.169.175; 13.G.169.240; 13.G.169.244;
13.G.172.228; 13.G.172.229; 13.G.172.230; 13.G.172.231; 13.G.172.236; 13.G.172.237;
13.G.172.238; 13.G.172.239; 13.G.172.154; 13.G.172.157; 13.G.172.166; 13.G.172.169;
35 13.G.172.172; 13.G.172.175; 13.G.172.240; 13.G.172.244; 13.G.175.228; 13.G.175.229;
13.G.175.230; 13.G.175.231; 13.G.175.236; 13.G.175.237; 13.G.175.238; 13.G.175.239;
13.G.175.154; 13.G.175.157; 13.G.175.166; 13.G.175.169; 13.G.175.172; 13.G.175.175;
13.G.175.240; 13.G.175.244; 13.G.240.228; 13.G.240.229; 13.G.240.230; 13.G.240.231;
13.G.240.236; 13.G.240.237; 13.G.240.238; 13.G.240.239; 13.G.240.154; 13.G.240.157;
40 13.G.240.166; 13.G.240.169; 13.G.240.172; 13.G.240.175; 13.G.240.240; 13.G.240.244;
13.G.244.228; 13.G.244.229; 13.G.244.230; 13.G.244.231; 13.G.244.236; 13.G.244.237;
13.G.244.238; 13.G.244.239; 13.G.244.154; 13.G.244.157; 13.G.244.166; 13.G.244.169;
13.G.244.172; 13.G.244.175; 13.G.244.240; 13.G.244.244;

45 Prodrugs of 13.I

13.I.228.228; 13.I.228.229; 13.I.228.230; 13.I.228.231; 13.I.228.236; 13.I.228.237;
13.I.228.238; 13.I.228.239; 13.I.228.154; 13.I.228.157; 13.I.228.166; 13.I.228.169;
13.I.228.172; 13.I.228.175; 13.I.228.240; 13.I.228.244; 13.I.229.228; 13.I.229.229;
13.I.229.230; 13.I.229.231; 13.I.229.236; 13.I.229.237; 13.I.229.238; 13.I.229.239;
5 13.I.229.154; 13.I.229.157; 13.I.229.166; 13.I.229.169; 13.I.229.172; 13.I.229.175;
13.I.229.240; 13.I.229.244; 13.I.230.228; 13.I.230.229; 13.I.230.230; 13.I.230.231;
13.I.230.236; 13.I.230.237; 13.I.230.238; 13.I.230.239; 13.I.230.154; 13.I.230.157;
13.I.230.166; 13.I.230.169; 13.I.230.172; 13.I.230.175; 13.I.230.240; 13.I.230.244;
13.I.231.228; 13.I.231.229; 13.I.231.230; 13.I.231.231; 13.I.231.236; 13.I.231.237;
10 13.I.231.238; 13.I.231.239; 13.I.231.154; 13.I.231.157; 13.I.231.166; 13.I.231.169;
13.I.231.172; 13.I.231.175; 13.I.231.240; 13.I.231.244; 13.I.236.228; 13.I.236.229;
13.I.236.230; 13.I.236.231; 13.I.236.236; 13.I.236.237; 13.I.236.238; 13.I.236.239;
13.I.236.154; 13.I.236.157; 13.I.236.166; 13.I.236.169; 13.I.236.172; 13.I.236.175;
13.I.236.240; 13.I.236.244; 13.I.237.228; 13.I.237.229; 13.I.237.230; 13.I.237.231;
15 13.I.237.236; 13.I.237.237; 13.I.237.238; 13.I.237.239; 13.I.237.154; 13.I.237.157;
13.I.237.166; 13.I.237.169; 13.I.237.172; 13.I.237.175; 13.I.237.240; 13.I.237.244;
13.I.238.228; 13.I.238.229; 13.I.238.230; 13.I.238.231; 13.I.238.236; 13.I.238.237;
13.I.238.238; 13.I.238.239; 13.I.238.154; 13.I.238.157; 13.I.238.166; 13.I.238.169;
13.I.238.172; 13.I.238.175; 13.I.238.240; 13.I.238.244; 13.I.239.228; 13.I.239.229;
20 13.I.239.230; 13.I.239.231; 13.I.239.236; 13.I.239.237; 13.I.239.238; 13.I.239.239;
13.I.239.154; 13.I.239.157; 13.I.239.166; 13.I.239.169; 13.I.239.172; 13.I.239.175;
13.I.239.240; 13.I.239.244; 13.I.154.228; 13.I.154.229; 13.I.154.230; 13.I.154.231;
13.I.154.236; 13.I.154.237; 13.I.154.238; 13.I.154.239; 13.I.154.154; 13.I.154.157;
13.I.154.166; 13.I.154.169; 13.I.154.172; 13.I.154.175; 13.I.154.240; 13.I.154.244;
25 13.I.157.228; 13.I.157.229; 13.I.157.230; 13.I.157.231; 13.I.157.236; 13.I.157.237;
13.I.157.238; 13.I.157.239; 13.I.157.154; 13.I.157.157; 13.I.157.166; 13.I.157.169;
13.I.157.172; 13.I.157.175; 13.I.157.240; 13.I.157.244; 13.I.166.228; 13.I.166.229;
13.I.166.230; 13.I.166.231; 13.I.166.236; 13.I.166.237; 13.I.166.238; 13.I.166.239;
13.I.166.154; 13.I.166.157; 13.I.166.166; 13.I.166.169; 13.I.166.172; 13.I.166.175;
30 13.I.166.240; 13.I.166.244; 13.I.169.228; 13.I.169.229; 13.I.169.230; 13.I.169.231;
13.I.169.236; 13.I.169.237; 13.I.169.238; 13.I.169.239; 13.I.169.154; 13.I.169.157;
13.I.169.166; 13.I.169.169; 13.I.169.172; 13.I.169.175; 13.I.169.240; 13.I.169.244;
13.I.172.228; 13.I.172.229; 13.I.172.230; 13.I.172.231; 13.I.172.236; 13.I.172.237;
13.I.172.238; 13.I.172.239; 13.I.172.154; 13.I.172.157; 13.I.172.166; 13.I.172.169;
35 13.I.172.172; 13.I.172.175; 13.I.172.240; 13.I.172.244; 13.I.175.228; 13.I.175.229;
13.I.175.230; 13.I.175.231; 13.I.175.236; 13.I.175.237; 13.I.175.238; 13.I.175.239;
13.I.175.154; 13.I.175.157; 13.I.175.166; 13.I.175.169; 13.I.175.172; 13.I.175.175;
13.I.175.240; 13.I.175.244; 13.I.240.228; 13.I.240.229; 13.I.240.230; 13.I.240.231;
13.I.240.236; 13.I.240.237; 13.I.240.238; 13.I.240.239; 13.I.240.154; 13.I.240.157;
40 13.I.240.166; 13.I.240.169; 13.I.240.172; 13.I.240.175; 13.I.240.240; 13.I.240.244;
13.I.244.228; 13.I.244.229; 13.I.244.230; 13.I.244.231; 13.I.244.236; 13.I.244.237;
13.I.244.238; 13.I.244.239; 13.I.244.154; 13.I.244.157; 13.I.244.166; 13.I.244.169;
13.I.244.172; 13.I.244.175; 13.I.244.240; 13.I.244.244;

45 Prodrugs of 13.I

13.J.228.228; 13.J.228.229; 13.J.228.230; 13.J.228.231; 13.J.228.236; 13.J.228.237;
13.J.228.238; 13.J.228.239; 13.J.228.154; 13.J.228.157; 13.J.228.166; 13.J.228.169;
13.J.228.172; 13.J.228.175; 13.J.228.240; 13.J.228.244; 13.J.229.228; 13.J.229.229;
13.J.229.230; 13.J.229.231; 13.J.229.236; 13.J.229.237; 13.J.229.238; 13.J.229.239;
5 13.J.229.154; 13.J.229.157; 13.J.229.166; 13.J.229.169; 13.J.229.172; 13.J.229.175;
13.J.229.240; 13.J.229.244; 13.J.230.228; 13.J.230.229; 13.J.230.230; 13.J.230.231;
13.J.230.236; 13.J.230.237; 13.J.230.238; 13.J.230.239; 13.J.230.154; 13.J.230.157;
13.J.230.166; 13.J.230.169; 13.J.230.172; 13.J.230.175; 13.J.230.240; 13.J.230.244;
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10 13.J.231.238; 13.J.231.239; 13.J.231.154; 13.J.231.157; 13.J.231.166; 13.J.231.169;
13.J.231.172; 13.J.231.175; 13.J.231.240; 13.J.231.244; 13.J.236.228; 13.J.236.229;
13.J.236.230; 13.J.236.231; 13.J.236.236; 13.J.236.237; 13.J.236.238; 13.J.236.239;
13.J.236.154; 13.J.236.157; 13.J.236.166; 13.J.236.169; 13.J.236.172; 13.J.236.175;
13.J.236.240; 13.J.236.244; 13.J.237.228; 13.J.237.229; 13.J.237.230; 13.J.237.231;
15 13.J.237.236; 13.J.237.237; 13.J.237.238; 13.J.237.239; 13.J.237.154; 13.J.237.157;
13.J.237.166; 13.J.237.169; 13.J.237.172; 13.J.237.175; 13.J.237.240; 13.J.237.244;
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13.J.238.238; 13.J.238.239; 13.J.238.154; 13.J.238.157; 13.J.238.166; 13.J.238.169;
13.J.238.172; 13.J.238.175; 13.J.238.240; 13.J.238.244; 13.J.239.228; 13.J.239.229;
20 13.J.239.230; 13.J.239.231; 13.J.239.236; 13.J.239.237; 13.J.239.238; 13.J.239.239;
13.J.239.154; 13.J.239.157; 13.J.239.166; 13.J.239.169; 13.J.239.172; 13.J.239.175;
13.J.239.240; 13.J.239.244; 13.J.154.228; 13.J.154.229; 13.J.154.230; 13.J.154.231;
13.J.154.236; 13.J.154.237; 13.J.154.238; 13.J.154.239; 13.J.154.154; 13.J.154.157;
13.J.154.166; 13.J.154.169; 13.J.154.172; 13.J.154.175; 13.J.154.240; 13.J.154.244;
25 13.J.157.228; 13.J.157.229; 13.J.157.230; 13.J.157.231; 13.J.157.236; 13.J.157.237;
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13.J.166.230; 13.J.166.231; 13.J.166.236; 13.J.166.237; 13.J.166.238; 13.J.166.239;
13.J.166.154; 13.J.166.157; 13.J.166.166; 13.J.166.169; 13.J.166.172; 13.J.166.175;
30 13.J.166.240; 13.J.166.244; 13.J.169.228; 13.J.169.229; 13.J.169.230; 13.J.169.231;
13.J.169.236; 13.J.169.237; 13.J.169.238; 13.J.169.239; 13.J.169.154; 13.J.169.157;
13.J.169.166; 13.J.169.169; 13.J.169.172; 13.J.169.175; 13.J.169.240; 13.J.169.244;
13.J.172.228; 13.J.172.229; 13.J.172.230; 13.J.172.231; 13.J.172.236; 13.J.172.237;
13.J.172.238; 13.J.172.239; 13.J.172.154; 13.J.172.157; 13.J.172.166; 13.J.172.169;
35 13.J.172.172; 13.J.172.175; 13.J.172.240; 13.J.172.244; 13.J.175.228; 13.J.175.229;
13.J.175.230; 13.J.175.231; 13.J.175.236; 13.J.175.237; 13.J.175.238; 13.J.175.239;
13.J.175.154; 13.J.175.157; 13.J.175.166; 13.J.175.169; 13.J.175.172; 13.J.175.175;
13.J.175.240; 13.J.175.244; 13.J.240.228; 13.J.240.229; 13.J.240.230; 13.J.240.231;
13.J.240.236; 13.J.240.237; 13.J.240.238; 13.J.240.239; 13.J.240.154; 13.J.240.157;
40 13.J.240.166; 13.J.240.169; 13.J.240.172; 13.J.240.175; 13.J.240.240; 13.J.240.244;
13.J.244.228; 13.J.244.229; 13.J.244.230; 13.J.244.231; 13.J.244.236; 13.J.244.237;
13.J.244.238; 13.J.244.239; 13.J.244.154; 13.J.244.157; 13.J.244.166; 13.J.244.169;
13.J.244.172; 13.J.244.175; 13.J.244.240; 13.J.244.244;

45 Prodrugs of 13.L

- 13.L.228.228; 13.L.228.229; 13.L.228.230; 13.L.228.231; 13.L.228.236; 13.L.228.237;
13.L.228.238; 13.L.228.239; 13.L.228.154; 13.L.228.157; 13.L.228.166; 13.L.228.169;
13.L.228.172; 13.L.228.175; 13.L.228.240; 13.L.228.244; 13.L.229.228; 13.L.229.229;
13.L.229.230; 13.L.229.231; 13.L.229.236; 13.L.229.237; 13.L.229.238; 13.L.229.239;
5 13.L.229.154; 13.L.229.157; 13.L.229.166; 13.L.229.169; 13.L.229.172; 13.L.229.175;
13.L.229.240; 13.L.229.244; 13.L.230.228; 13.L.230.229; 13.L.230.230; 13.L.230.231;
13.L.230.236; 13.L.230.237; 13.L.230.238; 13.L.230.239; 13.L.230.154; 13.L.230.157;
13.L.230.166; 13.L.230.169; 13.L.230.172; 13.L.230.175; 13.L.230.240; 13.L.230.244;
13.L.231.228; 13.L.231.229; 13.L.231.230; 13.L.231.231; 13.L.231.236; 13.L.231.237;
10 13.L.231.238; 13.L.231.239; 13.L.231.154; 13.L.231.157; 13.L.231.166; 13.L.231.169;
13.L.231.172; 13.L.231.175; 13.L.231.240; 13.L.231.244; 13.L.236.228; 13.L.236.229;
13.L.236.230; 13.L.236.231; 13.L.236.236; 13.L.236.237; 13.L.236.238; 13.L.236.239;
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15 13.L.237.236; 13.L.237.237; 13.L.237.238; 13.L.237.239; 13.L.237.154; 13.L.237.157;
13.L.237.166; 13.L.237.169; 13.L.237.172; 13.L.237.175; 13.L.237.240; 13.L.237.244;
13.L.238.228; 13.L.238.229; 13.L.238.230; 13.L.238.231; 13.L.238.236; 13.L.238.237;
13.L.238.238; 13.L.238.239; 13.L.238.154; 13.L.238.157; 13.L.238.166; 13.L.238.169;
13.L.238.172; 13.L.238.175; 13.L.238.240; 13.L.238.244; 13.L.239.228; 13.L.239.229;
20 13.L.239.230; 13.L.239.231; 13.L.239.236; 13.L.239.237; 13.L.239.238; 13.L.239.239;
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13.L.239.240; 13.L.239.244; 13.L.154.228; 13.L.154.229; 13.L.154.230; 13.L.154.231;
13.L.154.236; 13.L.154.237; 13.L.154.238; 13.L.154.239; 13.L.154.154; 13.L.154.157;
13.L.154.166; 13.L.154.169; 13.L.154.172; 13.L.154.175; 13.L.154.240; 13.L.154.244;
25 13.L.157.228; 13.L.157.229; 13.L.157.230; 13.L.157.231; 13.L.157.236; 13.L.157.237;
13.L.157.238; 13.L.157.239; 13.L.157.154; 13.L.157.157; 13.L.157.166; 13.L.157.169;
13.L.157.172; 13.L.157.175; 13.L.157.240; 13.L.157.244; 13.L.166.228; 13.L.166.229;
13.L.166.230; 13.L.166.231; 13.L.166.236; 13.L.166.237; 13.L.166.238; 13.L.166.239;
13.L.166.154; 13.L.166.157; 13.L.166.166; 13.L.166.169; 13.L.166.172; 13.L.166.175;
30 13.L.166.240; 13.L.166.244; 13.L.169.228; 13.L.169.229; 13.L.169.230; 13.L.169.231;
13.L.169.236; 13.L.169.237; 13.L.169.238; 13.L.169.239; 13.L.169.154; 13.L.169.157;
13.L.169.166; 13.L.169.169; 13.L.169.172; 13.L.169.175; 13.L.169.240; 13.L.169.244;
13.L.172.228; 13.L.172.229; 13.L.172.230; 13.L.172.231; 13.L.172.236; 13.L.172.237;
13.L.172.238; 13.L.172.239; 13.L.172.154; 13.L.172.157; 13.L.172.166; 13.L.172.169;
35 13.L.172.172; 13.L.172.175; 13.L.172.240; 13.L.172.244; 13.L.175.228; 13.L.175.229;
13.L.175.230; 13.L.175.231; 13.L.175.236; 13.L.175.237; 13.L.175.238; 13.L.175.239;
13.L.175.154; 13.L.175.157; 13.L.175.166; 13.L.175.169; 13.L.175.172; 13.L.175.175;
13.L.175.240; 13.L.175.244; 13.L.240.228; 13.L.240.229; 13.L.240.230; 13.L.240.231;
13.L.240.236; 13.L.240.237; 13.L.240.238; 13.L.240.239; 13.L.240.154; 13.L.240.157;
40 13.L.240.166; 13.L.240.169; 13.L.240.172; 13.L.240.175; 13.L.240.240; 13.L.240.244;
13.L.244.228; 13.L.244.229; 13.L.244.230; 13.L.244.231; 13.L.244.236; 13.L.244.237;
13.L.244.238; 13.L.244.239; 13.L.244.154; 13.L.244.157; 13.L.244.166; 13.L.244.169;
13.L.244.172; 13.L.244.175; 13.L.244.240; 13.L.244.244;

45 Prodrugs of 13.O

13.O.228.228; 13.O.228.229; 13.O.228.230; 13.O.228.231; 13.O.228.236; 13.O.228.237;
13.O.228.238; 13.O.228.239; 13.O.228.154; 13.O.228.157; 13.O.228.166; 13.O.228.169;
13.O.228.172; 13.O.228.175; 13.O.228.240; 13.O.228.244; 13.O.229.228; 13.O.229.229;
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5 13.O.229.154; 13.O.229.157; 13.O.229.166; 13.O.229.169; 13.O.229.172; 13.O.229.175;
13.O.229.240; 13.O.229.244; 13.O.230.228; 13.O.230.229; 13.O.230.230; 13.O.230.231;
13.O.230.236; 13.O.230.237; 13.O.230.238; 13.O.230.239; 13.O.230.154; 13.O.230.157;
13.O.230.166; 13.O.230.169; 13.O.230.172; 13.O.230.175; 13.O.230.240; 13.O.230.244;
13.O.231.228; 13.O.231.229; 13.O.231.230; 13.O.231.231; 13.O.231.236; 13.O.231.237;
10 13.O.231.238; 13.O.231.239; 13.O.231.154; 13.O.231.157; 13.O.231.166; 13.O.231.169;
13.O.231.172; 13.O.231.175; 13.O.231.240; 13.O.231.244; 13.O.236.228; 13.O.236.229;
13.O.236.230; 13.O.236.231; 13.O.236.236; 13.O.236.237; 13.O.236.238; 13.O.236.239;
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13.O.236.240; 13.O.236.244; 13.O.237.228; 13.O.237.229; 13.O.237.230; 13.O.237.231;
15 13.O.237.236; 13.O.237.237; 13.O.237.238; 13.O.237.239; 13.O.237.154; 13.O.237.157;
13.O.237.166; 13.O.237.169; 13.O.237.172; 13.O.237.175; 13.O.237.240; 13.O.237.244;
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13.O.238.172; 13.O.238.175; 13.O.238.240; 13.O.238.244; 13.O.239.228; 13.O.239.229;
20 13.O.239.230; 13.O.239.231; 13.O.239.236; 13.O.239.237; 13.O.239.238; 13.O.239.239;
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25 13.O.157.228; 13.O.157.229; 13.O.157.230; 13.O.157.231; 13.O.157.236; 13.O.157.237;
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13.O.157.172; 13.O.157.175; 13.O.157.240; 13.O.157.244; 13.O.166.228; 13.O.166.229;
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30 13.O.166.240; 13.O.166.244; 13.O.169.228; 13.O.169.229; 13.O.169.230; 13.O.169.231;
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35 13.O.172.172; 13.O.172.175; 13.O.172.240; 13.O.172.244; 13.O.175.228; 13.O.175.229;
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40 13.O.240.166; 13.O.240.169; 13.O.240.172; 13.O.240.175; 13.O.240.240; 13.O.240.244;
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13.O.244.238; 13.O.244.239; 13.O.244.154; 13.O.244.157; 13.O.244.166; 13.O.244.169;
13.O.244.172; 13.O.244.175; 13.O.244.240; 13.O.244.244;

45 Prodrugs of 13.P

- 13.P.228.228; 13.P.228.229; 13.P.228.230; 13.P.228.231; 13.P.228.236; 13.P.228.237;
 13.P.228.238; 13.P.228.239; 13.P.228.154; 13.P.228.157; 13.P.228.166; 13.P.228.169;
 13.P.228.172; 13.P.228.175; 13.P.228.240; 13.P.228.244; 13.P.229.228; 13.P.229.229;
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 5 13.P.229.154; 13.P.229.157; 13.P.229.166; 13.P.229.169; 13.P.229.172; 13.P.229.175;
 13.P.229.240; 13.P.229.244; 13.P.230.228; 13.P.230.229; 13.P.230.230; 13.P.230.231;
 13.P.230.236; 13.P.230.237; 13.P.230.238; 13.P.230.239; 13.P.230.154; 13.P.230.157;
 13.P.230.166; 13.P.230.169; 13.P.230.172; 13.P.230.175; 13.P.230.240; 13.P.230.244;
 10 13.P.231.228; 13.P.231.229; 13.P.231.230; 13.P.231.231; 13.P.231.236; 13.P.231.237;
 13.P.231.238; 13.P.231.239; 13.P.231.154; 13.P.231.157; 13.P.231.166; 13.P.231.169;
 13.P.231.172; 13.P.231.175; 13.P.231.240; 13.P.231.244; 13.P.236.228; 13.P.236.229;
 13.P.236.230; 13.P.236.231; 13.P.236.236; 13.P.236.237; 13.P.236.238; 13.P.236.239;
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 13.P.236.240; 13.P.236.244; 13.P.237.228; 13.P.237.229; 13.P.237.230; 13.P.237.231;
 15 13.P.237.236; 13.P.237.237; 13.P.237.238; 13.P.237.239; 13.P.237.154; 13.P.237.157;
 13.P.237.166; 13.P.237.169; 13.P.237.172; 13.P.237.175; 13.P.237.240; 13.P.237.244;
 13.P.238.228; 13.P.238.229; 13.P.238.230; 13.P.238.231; 13.P.238.236; 13.P.238.237;
 13.P.238.238; 13.P.238.239; 13.P.238.154; 13.P.238.157; 13.P.238.166; 13.P.238.169;
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 20 13.P.239.230; 13.P.239.231; 13.P.239.236; 13.P.239.237; 13.P.239.238; 13.P.239.239;
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 13.P.239.240; 13.P.239.244; 13.P.154.228; 13.P.154.229; 13.P.154.230; 13.P.154.231;
 13.P.154.236; 13.P.154.237; 13.P.154.238; 13.P.154.239; 13.P.154.154; 13.P.154.157;
 13.P.154.166; 13.P.154.169; 13.P.154.172; 13.P.154.175; 13.P.154.240; 13.P.154.244;
 25 13.P.157.228; 13.P.157.229; 13.P.157.230; 13.P.157.231; 13.P.157.236; 13.P.157.237;
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 13.P.166.230; 13.P.166.231; 13.P.166.236; 13.P.166.237; 13.P.166.238; 13.P.166.239;
 13.P.166.154; 13.P.166.157; 13.P.166.166; 13.P.166.169; 13.P.166.172; 13.P.166.175;
 30 13.P.166.240; 13.P.166.244; 13.P.169.228; 13.P.169.229; 13.P.169.230; 13.P.169.231;
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 35 13.P.172.172; 13.P.172.175; 13.P.172.240; 13.P.172.244; 13.P.175.228; 13.P.175.229;
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 13.P.175.154; 13.P.175.157; 13.P.175.166; 13.P.175.169; 13.P.175.172; 13.P.175.175;
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 13.P.240.236; 13.P.240.237; 13.P.240.238; 13.P.240.239; 13.P.240.154; 13.P.240.157;
 40 13.P.240.166; 13.P.240.169; 13.P.240.172; 13.P.240.175; 13.P.240.240; 13.P.240.244;
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 13.P.244.238; 13.P.244.239; 13.P.244.154; 13.P.244.157; 13.P.244.166; 13.P.244.169;
 13.P.244.172; 13.P.244.175; 13.P.244.240; 13.P.244.244;

45 Prodrugs of 13.U

13.U.228.228; 13.U.228.229; 13.U.228.230; 13.U.228.231; 13.U.228.236; 13.U.228.237;
13.U.228.238; 13.U.228.239; 13.U.228.154; 13.U.228.157; 13.U.228.166; 13.U.228.169;
13.U.228.172; 13.U.228.175; 13.U.228.240; 13.U.228.244; 13.U.229.228; 13.U.229.229;
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5 13.U.229.154; 13.U.229.157; 13.U.229.166; 13.U.229.169; 13.U.229.172; 13.U.229.175;
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13.U.230.166; 13.U.230.169; 13.U.230.172; 13.U.230.175; 13.U.230.240; 13.U.230.244;
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10 13.U.231.238; 13.U.231.239; 13.U.231.154; 13.U.231.157; 13.U.231.166; 13.U.231.169;
13.U.231.172; 13.U.231.175; 13.U.231.240; 13.U.231.244; 13.U.236.228; 13.U.236.229;
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13.U.236.154; 13.U.236.157; 13.U.236.166; 13.U.236.169; 13.U.236.172; 13.U.236.175;
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15 13.U.237.236; 13.U.237.237; 13.U.237.238; 13.U.237.239; 13.U.237.154; 13.U.237.157;
13.U.237.166; 13.U.237.169; 13.U.237.172; 13.U.237.175; 13.U.237.240; 13.U.237.244;
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13.U.154.166; 13.U.154.169; 13.U.154.172; 13.U.154.175; 13.U.154.240; 13.U.154.244;
25 13.U.157.228; 13.U.157.229; 13.U.157.230; 13.U.157.231; 13.U.157.236; 13.U.157.237;
13.U.157.238; 13.U.157.239; 13.U.157.154; 13.U.157.157; 13.U.157.166; 13.U.157.169;
13.U.157.172; 13.U.157.175; 13.U.157.240; 13.U.157.244; 13.U.166.228; 13.U.166.229;
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30 13.U.166.240; 13.U.166.244; 13.U.169.228; 13.U.169.229; 13.U.169.230; 13.U.169.231;
13.U.169.236; 13.U.169.237; 13.U.169.238; 13.U.169.239; 13.U.169.154; 13.U.169.157;
13.U.169.166; 13.U.169.169; 13.U.169.172; 13.U.169.175; 13.U.169.240; 13.U.169.244;
13.U.172.228; 13.U.172.229; 13.U.172.230; 13.U.172.231; 13.U.172.236; 13.U.172.237;
13.U.172.238; 13.U.172.239; 13.U.172.154; 13.U.172.157; 13.U.172.166; 13.U.172.169;
35 13.U.172.172; 13.U.172.175; 13.U.172.240; 13.U.172.244; 13.U.175.228; 13.U.175.229;
13.U.175.230; 13.U.175.231; 13.U.175.236; 13.U.175.237; 13.U.175.238; 13.U.175.239;
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13.U.175.240; 13.U.175.244; 13.U.240.228; 13.U.240.229; 13.U.240.230; 13.U.240.231;
13.U.240.236; 13.U.240.237; 13.U.240.238; 13.U.240.239; 13.U.240.154; 13.U.240.157;
40 13.U.240.166; 13.U.240.169; 13.U.240.172; 13.U.240.175; 13.U.240.240; 13.U.240.244;
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13.U.244.238; 13.U.244.239; 13.U.244.154; 13.U.244.157; 13.U.244.166; 13.U.244.169;
13.U.244.172; 13.U.244.175; 13.U.244.240; 13.U.244.244;

45 Prodrugs of 13.W

13.W.228.228; 13.W.228.229; 13.W.228.230; 13.W.228.231; 13.W.228.236;
 13.W.228.237; 13.W.228.238; 13.W.228.239; 13.W.228.154; 13.W.228.157; 13.W.228.166;
 13.W.228.169; 13.W.228.172; 13.W.228.175; 13.W.228.240; 13.W.228.244; 13.W.229.228;
 13.W.229.229; 13.W.229.230; 13.W.229.231; 13.W.229.236; 13.W.229.237; 13.W.229.238;
 5 13.W.229.239; 13.W.229.154; 13.W.229.157; 13.W.229.166; 13.W.229.169; 13.W.229.172;
 13.W.229.175; 13.W.229.240; 13.W.229.244; 13.W.230.228; 13.W.230.229; 13.W.230.230;
 13.W.230.231; 13.W.230.236; 13.W.230.237; 13.W.230.238; 13.W.230.239; 13.W.230.154;
 13.W.230.157; 13.W.230.166; 13.W.230.169; 13.W.230.172; 13.W.230.175; 13.W.230.240;
 13.W.230.244; 13.W.231.228; 13.W.231.229; 13.W.231.230; 13.W.231.231; 13.W.231.236;
 10 13.W.231.237; 13.W.231.238; 13.W.231.239; 13.W.231.154; 13.W.231.157; 13.W.231.166;
 13.W.231.169; 13.W.231.172; 13.W.231.175; 13.W.231.240; 13.W.231.244; 13.W.236.228;
 13.W.236.229; 13.W.236.230; 13.W.236.231; 13.W.236.236; 13.W.236.237; 13.W.236.238;
 13.W.236.239; 13.W.236.154; 13.W.236.157; 13.W.236.166; 13.W.236.169; 13.W.236.172;
 13.W.236.175; 13.W.236.240; 13.W.236.244; 13.W.237.228; 13.W.237.229; 13.W.237.230;
 15 13.W.237.231; 13.W.237.236; 13.W.237.237; 13.W.237.238; 13.W.237.239; 13.W.237.154;
 13.W.237.157; 13.W.237.166; 13.W.237.169; 13.W.237.172; 13.W.237.175; 13.W.237.240;
 13.W.237.244; 13.W.238.228; 13.W.238.229; 13.W.238.230; 13.W.238.231; 13.W.238.236;
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 13.W.238.169; 13.W.238.172; 13.W.238.175; 13.W.238.240; 13.W.238.244; 13.W.239.228;
 20 13.W.239.229; 13.W.239.230; 13.W.239.231; 13.W.239.236; 13.W.239.237; 13.W.239.238;
 13.W.239.239; 13.W.239.154; 13.W.239.157; 13.W.239.166; 13.W.239.169; 13.W.239.172;
 13.W.239.175; 13.W.239.240; 13.W.239.244; 13.W.154.228; 13.W.154.229; 13.W.154.230;
 13.W.154.231; 13.W.154.236; 13.W.154.237; 13.W.154.238; 13.W.154.239; 13.W.154.154;
 13.W.154.157; 13.W.154.166; 13.W.154.169; 13.W.154.172; 13.W.154.175; 13.W.154.240;
 25 13.W.154.244; 13.W.157.228; 13.W.157.229; 13.W.157.230; 13.W.157.231; 13.W.157.236;
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 13.W.157.169; 13.W.157.172; 13.W.157.175; 13.W.157.240; 13.W.157.244; 13.W.166.228;
 13.W.166.229; 13.W.166.230; 13.W.166.231; 13.W.166.236; 13.W.166.237; 13.W.166.238;
 13.W.166.239; 13.W.166.154; 13.W.166.157; 13.W.166.166; 13.W.166.169; 13.W.166.172;
 30 13.W.166.175; 13.W.166.240; 13.W.166.244; 13.W.169.228; 13.W.169.229; 13.W.169.230;
 13.W.169.231; 13.W.169.236; 13.W.169.237; 13.W.169.238; 13.W.169.239; 13.W.169.154;
 13.W.169.157; 13.W.169.166; 13.W.169.169; 13.W.169.172; 13.W.169.175; 13.W.169.240;
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 13.W.172.237; 13.W.172.238; 13.W.172.239; 13.W.172.154; 13.W.172.157; 13.W.172.166;
 35 13.W.172.169; 13.W.172.172; 13.W.172.175; 13.W.172.240; 13.W.172.244; 13.W.175.228;
 13.W.175.229; 13.W.175.230; 13.W.175.231; 13.W.175.236; 13.W.175.237; 13.W.175.238;
 13.W.175.239; 13.W.175.154; 13.W.175.157; 13.W.175.166; 13.W.175.169; 13.W.175.172;
 13.W.175.175; 13.W.175.240; 13.W.175.244; 13.W.240.228; 13.W.240.229; 13.W.240.230;
 13.W.240.231; 13.W.240.236; 13.W.240.237; 13.W.240.238; 13.W.240.239; 13.W.240.154;
 40 13.W.240.157; 13.W.240.166; 13.W.240.169; 13.W.240.172; 13.W.240.175; 13.W.240.240;
 13.W.240.244; 13.W.244.228; 13.W.244.229; 13.W.244.230; 13.W.244.231; 13.W.244.236;
 13.W.244.237; 13.W.244.238; 13.W.244.239; 13.W.244.154; 13.W.244.157; 13.W.244.166;
 13.W.244.169; 13.W.244.172; 13.W.244.175; 13.W.244.240; 13.W.244.244;

45 Prodrugs of 13.Y

13.Y.228.228; 13.Y.228.229; 13.Y.228.230; 13.Y.228.231; 13.Y.228.236; 13.Y.228.237;
 13.Y.228.238; 13.Y.228.239; 13.Y.228.154; 13.Y.228.157; 13.Y.228.166; 13.Y.228.169;
 13.Y.228.172; 13.Y.228.175; 13.Y.228.240; 13.Y.228.244; 13.Y.229.228; 13.Y.229.229;
 13.Y.229.230; 13.Y.229.231; 13.Y.229.236; 13.Y.229.237; 13.Y.229.238; 13.Y.229.239;
 5 13.Y.229.154; 13.Y.229.157; 13.Y.229.166; 13.Y.229.169; 13.Y.229.172; 13.Y.229.175;
 13.Y.229.240; 13.Y.229.244; 13.Y.230.228; 13.Y.230.229; 13.Y.230.230; 13.Y.230.231;
 13.Y.230.236; 13.Y.230.237; 13.Y.230.238; 13.Y.230.239; 13.Y.230.154; 13.Y.230.157;
 13.Y.230.166; 13.Y.230.169; 13.Y.230.172; 13.Y.230.175; 13.Y.230.240; 13.Y.230.244;
 10 13.Y.231.228; 13.Y.231.229; 13.Y.231.230; 13.Y.231.231; 13.Y.231.236; 13.Y.231.237;
 13.Y.231.238; 13.Y.231.239; 13.Y.231.154; 13.Y.231.157; 13.Y.231.166; 13.Y.231.169;
 13.Y.231.172; 13.Y.231.175; 13.Y.231.240; 13.Y.231.244; 13.Y.236.228; 13.Y.236.229;
 13.Y.236.230; 13.Y.236.231; 13.Y.236.236; 13.Y.236.237; 13.Y.236.238; 13.Y.236.239;
 13.Y.236.154; 13.Y.236.157; 13.Y.236.166; 13.Y.236.169; 13.Y.236.172; 13.Y.236.175;
 13.Y.236.240; 13.Y.236.244; 13.Y.237.228; 13.Y.237.229; 13.Y.237.230; 13.Y.237.231;
 15 13.Y.237.236; 13.Y.237.237; 13.Y.237.238; 13.Y.237.239; 13.Y.237.154; 13.Y.237.157;
 13.Y.237.166; 13.Y.237.169; 13.Y.237.172; 13.Y.237.175; 13.Y.237.240; 13.Y.237.244;
 13.Y.238.228; 13.Y.238.229; 13.Y.238.230; 13.Y.238.231; 13.Y.238.236; 13.Y.238.237;
 13.Y.238.238; 13.Y.238.239; 13.Y.238.154; 13.Y.238.157; 13.Y.238.166; 13.Y.238.169;
 13.Y.238.172; 13.Y.238.175; 13.Y.238.240; 13.Y.238.244; 13.Y.239.228; 13.Y.239.229;
 20 13.Y.239.230; 13.Y.239.231; 13.Y.239.236; 13.Y.239.237; 13.Y.239.238; 13.Y.239.239;
 13.Y.239.154; 13.Y.239.157; 13.Y.239.166; 13.Y.239.169; 13.Y.239.172; 13.Y.239.175;
 13.Y.239.240; 13.Y.239.244; 13.Y.154.228; 13.Y.154.229; 13.Y.154.230; 13.Y.154.231;
 13.Y.154.236; 13.Y.154.237; 13.Y.154.238; 13.Y.154.239; 13.Y.154.154; 13.Y.154.157;
 13.Y.154.166; 13.Y.154.169; 13.Y.154.172; 13.Y.154.175; 13.Y.154.240; 13.Y.154.244;
 25 13.Y.157.228; 13.Y.157.229; 13.Y.157.230; 13.Y.157.231; 13.Y.157.236; 13.Y.157.237;
 13.Y.157.238; 13.Y.157.239; 13.Y.157.154; 13.Y.157.157; 13.Y.157.166; 13.Y.157.169;
 13.Y.157.172; 13.Y.157.175; 13.Y.157.240; 13.Y.157.244; 13.Y.166.228; 13.Y.166.229;
 13.Y.166.230; 13.Y.166.231; 13.Y.166.236; 13.Y.166.237; 13.Y.166.238; 13.Y.166.239;
 13.Y.166.154; 13.Y.166.157; 13.Y.166.166; 13.Y.166.169; 13.Y.166.172; 13.Y.166.175;
 30 13.Y.166.240; 13.Y.166.244; 13.Y.169.228; 13.Y.169.229; 13.Y.169.230; 13.Y.169.231;
 13.Y.169.236; 13.Y.169.237; 13.Y.169.238; 13.Y.169.239; 13.Y.169.154; 13.Y.169.157;
 13.Y.169.166; 13.Y.169.169; 13.Y.169.172; 13.Y.169.175; 13.Y.169.240; 13.Y.169.244;
 13.Y.172.228; 13.Y.172.229; 13.Y.172.230; 13.Y.172.231; 13.Y.172.236; 13.Y.172.237;
 13.Y.172.238; 13.Y.172.239; 13.Y.172.154; 13.Y.172.157; 13.Y.172.166; 13.Y.172.169;
 35 13.Y.172.172; 13.Y.172.175; 13.Y.172.240; 13.Y.172.244; 13.Y.175.228; 13.Y.175.229;
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 13.Y.175.240; 13.Y.175.244; 13.Y.240.228; 13.Y.240.229; 13.Y.240.230; 13.Y.240.231;
 13.Y.240.236; 13.Y.240.237; 13.Y.240.238; 13.Y.240.239; 13.Y.240.154; 13.Y.240.157;
 40 13.Y.240.166; 13.Y.240.169; 13.Y.240.172; 13.Y.240.175; 13.Y.240.240; 13.Y.240.244;
 13.Y.244.228; 13.Y.244.229; 13.Y.244.230; 13.Y.244.231; 13.Y.244.236; 13.Y.244.237;
 13.Y.244.238; 13.Y.244.239; 13.Y.244.154; 13.Y.244.157; 13.Y.244.166; 13.Y.244.169;
 13.Y.244.172; 13.Y.244.175; 13.Y.244.240; 13.Y.244.244;

Prodrugs of 14.AH

- 14.AH.4.157; 14.AH.4.158; 14.AH.4.196; 14.AH.4.223; 14.AH.4.240; 14.AH.4.244;
 14.AH.4.243; 14.AH.4.247; 14.AH.5.157; 14.AH.5.158; 14.AH.5.196; 14.AH.5.223;
 5 14.AH.5.240; 14.AH.5.244; 14.AH.5.243; 14.AH.5.247; 14.AH.7.157; 14.AH.7.158;
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 14.Cl.240.196; 14.Cl.240.223; 14.Cl.240.240; 14.Cl.240.244; 14.Cl.240.243; 14.Cl.240.247;
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14.Cl.244.243; 14.Cl.244.247; 14.Cl.247.157; 14.Cl.247.158; 14.Cl.247.196; 14.Cl.247.223;
14.Cl.247.240; 14.Cl.247.244; 14.Cl.247.243; 14.Cl.247.247;

Prodrugs of 14.CO

- 5 14.CO.4.157; 14.CO.4.158; 14.CO.4.196; 14.CO.4.223; 14.CO.4.240; 14.CO.4.244;
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14.CO.26.157; 14.CO.26.158; 14.CO.26.196; 14.CO.26.223; 14.CO.26.240; 14.CO.26.244;
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14.CO.55.240; 14.CO.55.244; 14.CO.55.243; 14.CO.55.247; 14.CO.56.157; 14.CO.56.158;
20 14.CO.56.196; 14.CO.56.223; 14.CO.56.240; 14.CO.56.244; 14.CO.56.243; 14.CO.56.247;
14.CO.157.157; 14.CO.157.158; 14.CO.157.196; 14.CO.157.223; 14.CO.157.240;
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14.CO.240.158; 14.CO.240.196; 14.CO.240.223; 14.CO.240.240; 14.CO.240.244;
14.CO.240.243; 14.CO.240.247; 14.CO.244.157; 14.CO.244.158; 14.CO.244.196;
14.CO.244.223; 14.CO.244.240; 14.CO.244.244; 14.CO.244.243; 14.CO.244.247;
14.CO.4.157; 14.CO.4.158; 14.CO.4.196; 14.CO.4.223; 14.CO.4.240; 14.CO.4.244;
30 14.CO.4.243; 14.CO.4.247;

Recursive Substituents

Selected substituents within the compounds of the invention are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number of compounds may be present in any given embodiment. For example, R^x contains a R^y substituent. R^y can be R^2 , which in turn can be R^3 . If R^3 is selected to be R^{3c} , then a second instance of R^x can be selected. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by way of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

By way of example and not limitation, W^3 , R^y and R^3 are all recursive substituents in certain embodiments. Typically, each of these may independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given embodiment. More typically, each of these may independently occur 12 or fewer times in a given embodiment. More typically yet, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times and R^3 will occur 0 to 10 times in a given embodiment. Even more typically, W^3 will occur 0 to 6 times, R^y will occur 0 to 4 times and R^3 will occur 0 to 8 times in a given embodiment.

Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an embodiment of the invention, the total number will be determined as set forth above.

Protecting Groups

In the context of the present invention, embodiments of protecting groups include prodrug moieties and chemical protecting groups.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, i.e. routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PRT" will be dependent upon the chemistry of the reaction to be protected against (e.g.,

acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PRT groups do not need to be, and generally are not, the same if the compound is substituted with multiple PRT. In general, PRT will be used to protect functional groups such as carboxyl, hydroxyl or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

Various functional groups of the compounds of the invention may be protection. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) are embodiments of "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

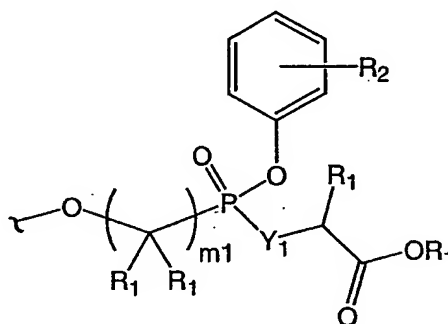
A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; "Protecting Groups" (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

Ether- and Ester-forming protecting groups

Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphoramidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

The phosphonate moieties of the compounds of the invention may or may not be prodrug moieties, i.e. they may or may not be susceptible to hydrolytic or enzymatic cleavage or modification. Certain phosphonate moieties are stable under most or nearly all metabolic conditions. For example, a dialkylphosphonate, where the alkyl groups are two or more
 5 carbons, may have appreciable stability *in vivo* due to a slow rate of hydrolysis.

Within the context of phosphonate prodrug moieties, a large number of structurally-diverse prodrugs have been described for phosphonic acids (Freeman and Ross in Progress in Medicinal Chemistry 34: 112-147 (1997) and are included within the scope of the present invention. An exemplary embodiment of a phosphonate ester-forming group is the phenyl
 10 carbocycle in substructure A₃ having the formula:



wherein m₁ is 1, 2, 3, 4, 5, 6, 7 or 8, and the phenyl carbocycle is substituted with 0 to 3 R₂ groups. Also, in this embodiment, where Y₁ is O, a lactate ester is formed. Alternatively, where Y₁ is N(R₂), N(OR₂) or N(N(R₂)₂), then phosphoramidate esters result.
 15 R₁ may be H or C₁-C₁₂ alkyl. The corollary exemplary substructure A³ is included in the invention with Y¹, R¹ and R² substituents.

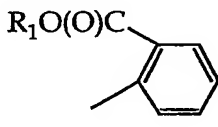
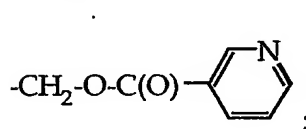
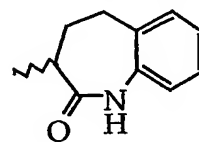
In its ester-forming role, a protecting group typically is bound to any acidic group such as, by way of example and not limitation, a -CO₂H or -C(S)OH group, thereby resulting in -CO₂R^x where R^x is defined herein. Also, R^x for example includes the
 20 enumerated ester groups of WO 95/07920.

Examples of protecting groups include:

C₃-C₁₂ heterocycle (described above) or aryl. These aromatic groups optionally are polycyclic or monocyclic. Examples include phenyl, spiryl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl,
 25 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 1-, 2-, 3- and 4-pyridinyl, and 1-, 2-, 4- and 5-pyrimidinyl,

C₃-C₁₂ heterocycle or aryl substituted with halo, R¹, R¹-O-C₁-C₁₂ alkylene, C₁-C₁₂ alkoxy, CN, NO₂, OH, carboxy, carboxyester, thiol, thioester, C₁-C₁₂ haloalkyl (1-6 halogen atoms), C₂-C₁₂ alkenyl or C₂-C₁₂ alkynyl. Such groups include 2-, 3- and 4-alkoxyphenyl (C₁-C₁₂ alkyl), 2-, 3- and 4-methoxyphenyl, 2-, 3- and 4-ethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl, 2-, 3- and 4-methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl and 2-, 3- and 4-chlorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-biscarboxyethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 3,5-difluorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C₁-C₁₂ alkyl including 4-trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C₁-C₁₂ alkyl including 4-trifluoromethylbenzyl and 2-, 3- and 4-trichloromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 4-N-methylpiperidiny, 3-N-methylpiperidiny, 1-ethylpiperazinyl, benzyl, alkylsalicylphenyl (C₁-C₄ alkyl, including 2-, 3- and 4-ethylsalicylphenyl), 2-, 3- and 4-acetylphenyl, 1,8-dihydroxynaphthyl (-C₁₀H₆-OH) and aryloxy ethyl [C₆-C₉ aryl (including phenoxy ethyl)], 2,2'-dihydroxybiphenyl, 2-, 3- and 4-N,N-dialkylaminophenol, -C₆H₄CH₂-N(CH₃)₂,

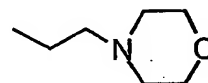
20 trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C₁₋₄ alkyl);



; C₄ - C₈ esters of 2-carboxyphenyl; and C₁-C₄ alkylene-C₃-C₆ aryl (including benzyl, -CH₂-pyrrolyl, -CH₂-thienyl, -CH₂-imidazolyl, -CH₂-oxazolyl, -CH₂-isoxazolyl, -CH₂-thiazolyl, -CH₂-isothiazolyl, -CH₂-pyrazolyl, -CH₂-pyridinyl and -CH₂-pyrimidinyl) substituted in the aryl moiety by 3 to 5 halogen atoms or 1 to 2 atoms or groups selected from halogen, C₁-C₁₂ alkoxy (including methoxy and ethoxy), cyano, nitro, OH, C₁-C₁₂ haloalkyl (1 to 6 halogen atoms; including -CH₂CCl₃), C₁-C₁₂ alkyl (including methyl and ethyl), C₂-C₁₂ alkenyl or C₂-C₁₂ alkynyl; alkoxy ethyl [C₁-C₆

alkyl including $-\text{CH}_2\text{CH}_2\text{OCH}_3$ (methoxy ethyl)]; alkyl substituted by any of the groups set forth above for aryl, in particular OH or by 1 to 3 halo atoms (including $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{CH}_3$, $-(\text{CH}_2)_2\text{CH}_3$, $-(\text{CH}_2)_3\text{CH}_3$, $-(\text{CH}_2)_4\text{CH}_3$, -

$(\text{CH}_2)_5\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{CF}_3$, and $-\text{CH}_2\text{CCl}_3$);



- 5 propylmorpholino, 2,3-dihydro-6-hydroxyindene, sesamol, catechol monoester, $-\text{CH}_2\text{C}(\text{O})\text{N}(\text{R}^1)_2$, $-\text{CH}_2\text{S}(\text{O})(\text{R}^1)$, $-\text{CH}_2\text{S}(\text{O})_2(\text{R}^1)$, $-\text{CH}_2\text{CH}(\text{OC}(\text{O})\text{CH}_2\text{R}^1)\text{CH}_2\text{OC}(\text{O})\text{CH}_2\text{R}^1$, cholesteryl, enolpyruvate ($\text{HOOC}-\text{C}(\text{=CH}_2)-$), glycerol;

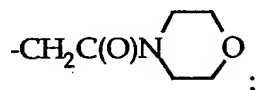
a 5 or 6 carbon monosaccharide, disaccharide or oligosaccharide (3 to 9 monosaccharide residues);

- 10 triglycerides such as α -D- β -diglycerides (wherein the fatty acids composing glyceride lipids generally are naturally occurring saturated or unsaturated C_{6-26} , C_{6-18} or C_{6-10} fatty acids such as linoleic, lauric, myristic, palmitic, stearic, oleic, palmitoleic, linolenic and the like fatty acids) linked to acyl of the parental compounds herein through a glyceryl oxygen of the triglyceride;

- 15 phospholipids linked to the carboxyl group through the phosphate of the phospholipid;

phthalidyl (shown in Fig. 1 of Clayton et al., *Antimicrob. Agents Chemo.* (1974) 5(6):670-671;

- 20 cyclic carbonates such as (5- R_d -2-oxo-1,3-dioxolen-4-yl) methyl esters (Sakamoto et al., *Chem. Pharm. Bull.* (1984) 32(6)2241-2248) where R_d is R_1 , R_4 or aryl; and



The hydroxyl groups of the compounds of this invention optionally are substituted with one of groups III, IV or V disclosed in WO 94/21604, or with isopropyl.

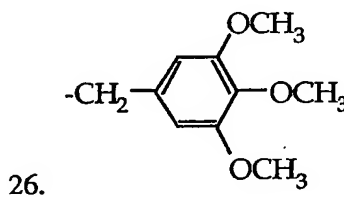
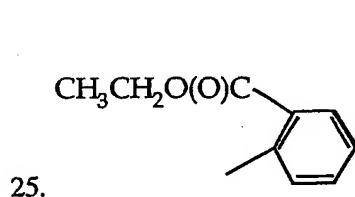
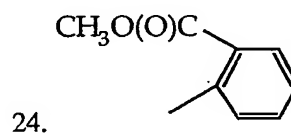
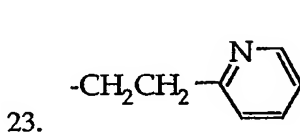
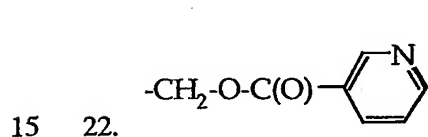
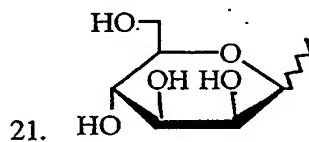
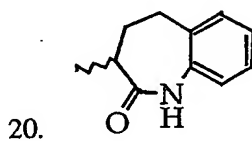
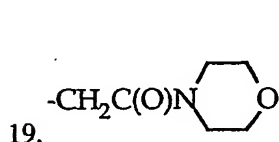
- 25 As further embodiments, Table A lists examples of protecting group ester moieties that for example can be bonded via oxygen to $-\text{C}(\text{O})\text{O}-$ and $-\text{P}(\text{O})(\text{O}-)_2$ groups. Several amidates also are shown, which are bound directly to $-\text{C}(\text{O})-$ or $-\text{P}(\text{O})_2$. Esters of structures 1-5, 8-10 and 16, 17, 19-22 are synthesized by reacting the compound herein having a free hydroxyl with the corresponding halide (chloride or acyl chloride and the like) and N,N-dicyclohexyl-N-morpholine carboxamidine (or another base such as DBU, triethylamine, CsCO_3 , N,N-

dimethylaniline and the like) in DMF (or other solvent such as acetonitrile or N-methylpyrrolidone). When the compound to be protected is a phosphonate, the esters of structures 5-7, 11, 12, 21, and 23-26 are synthesized by reaction of the alcohol or alkoxide salt (or the corresponding amines in the case of compounds such as 13, 14 and 15) with the

5 monochlorophosphonate or dichlorophosphonate (or another activated phosphonate).

TABLE A

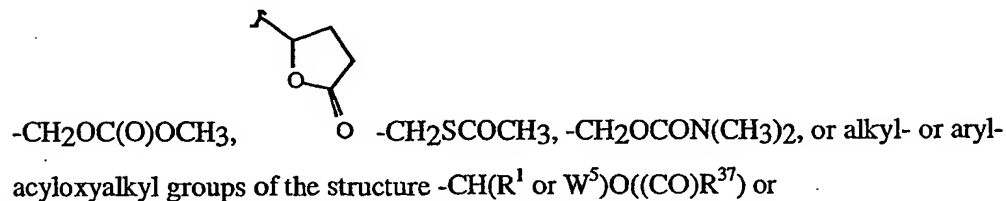
- | | |
|--|--|
| 1. $-\text{CH}_2-\text{C}(\text{O})-\text{N}(\text{R}_1)_2^*$ | 10. $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{C}(\text{CH}_3)_3$ |
| 2. $-\text{CH}_2-\text{S}(\text{O})(\text{R}_1)$ | 11. $-\text{CH}_2-\text{CCl}_3$ |
| 5 3. $-\text{CH}_2-\text{S}(\text{O})_2(\text{R}_1)$ | 12. $-\text{C}_6\text{H}_5$ |
| 4. $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{CH}_2-\text{C}_6\text{H}_5$ | 13. $-\text{NH}-\text{CH}_2-\text{C}(\text{O})\text{O}-\text{CH}_2\text{CH}_3$ |
| 5. 3-cholesteryl | 14. $-\text{N}(\text{CH}_3)-\text{CH}_2-\text{C}(\text{O})\text{O}-\text{CH}_2\text{CH}_3$ |
| 6. 3-pyridyl | 15. $-\text{NHR}_1$ |
| 7. N-ethylmorpholino | 16. $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{C}_{10}\text{H}_{15}$ |
| 10 8. $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{C}_6\text{H}_5$ | 17. $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{CH}(\text{CH}_3)_2$ |
| 9. $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{CH}_2\text{CH}_3$ | 18. $-\text{CH}_2-\text{C}\equiv\text{H}(\text{OC}(\text{O})\text{CH}_2\text{R}_1)-\text{CH}_2-(\text{OC}(\text{O})\text{CH}_2\text{R}_1)^*$ |



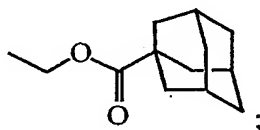
- chiral center is (R), (S) or racemate.

Other esters that are suitable for use herein are described in EP 632048.

20 Protecting groups also includes "double ester" forming profunctionalities such as



-CH(R¹ or W⁵)((CO)OR³⁸) (linked to oxygen of the acidic group) wherein R³⁷ and R³⁸ are alkyl, aryl, or alkylaryl groups (see U.S. Patent No. 4,968,788). Frequently R³⁷ and R³⁸ are bulky groups such as branched alkyl, ortho-substituted aryl, meta-substituted aryl, or combinations thereof, including normal, secondary, iso- and tertiary alkyls of 1-6 carbon atoms. An example is the pivaloyloxymethyl group. These are of particular use with prodrugs for oral administration. Examples of such useful protecting groups are alkylacyloxymethyl esters and their derivatives, including -



CH(CH₂CH₂OCH₃)OC(O)C(CH₃)₃,

-CH₂OC(O)C₁₀H₁₅, -CH₂OC(O)C(CH₃)₃, -CH(CH₂OCH₃)OC(O)C(CH₃)₃,

10 -CH(CH(CH₃)₂)OC(O)C(CH₃)₃, -CH₂OC(O)CH₂CH(CH₃)₂, -CH₂OC(O)C₆H₁₁,

-CH₂OC(O)C₆H₅, -CH₂OC(O)C₁₀H₁₅, -CH₂OC(O)CH₂CH₃, -CH₂OC(O)CH(CH₃)₂,

-CH₂OC(O)C(CH₃)₃ and -CH₂OC(O)CH₂C₆H₅.

For prodrug purposes, the ester typically chosen is one heretofore used for antibiotic drugs, in particular the cyclic carbonates, double esters, or the phthalidyl, aryl or alkyl esters.

15 In some embodiments the protected acidic group is an ester of the acidic group and is the residue of a hydroxyl-containing functionality. In other embodiments, an amino compound is used to protect the acid functionality. The residues of suitable hydroxyl or amino-containing functionalities are set forth above or are found in WO 95/07920. Of particular interest are the residues of amino acids, amino acid esters, polypeptides, or aryl alcohols. Typical amino acid, polypeptide and carboxyl-esterified amino acid residues are described on pages 11-18 and related text of WO 95/07920 as groups L1 or L2. WO 95/07920 expressly teaches the amidates of phosphonic acids, but it will be understood that such amidates are formed with any of the acid groups set forth herein and the amino acid residues set forth in WO 95/07920.

25 Typical esters for protecting acidic functionalities are also described in WO 95/07920, again understanding that the same esters can be formed with the acidic groups herein as with the phosphonate of the '920 publication. Typical ester groups are defined at least on WO 95/07920 pages 89-93 (under R³¹ or R³⁵), the table on page 105, and pages 21-23 (as R). Of particular interest are esters of unsubstituted aryl such as phenyl or arylalkyl such benzyl, or hydroxy-, halo-, alkoxy-, carboxy- and/or alkylestercarboxy-substituted aryl or alkylaryl,

30

especially phenyl, ortho-ethoxyphenyl, or C₁-C₄ alkylestercarboxyphenyl (salicylate C₁-C₁₂ alkylesters).

The protected acidic groups, particularly when using the esters or amides of WO 95/07920, are useful as prodrugs for oral administration. However, it is not essential that the acidic group be protected in order for the compounds of this invention to be effectively administered by the oral route. When the compounds of the invention having protected groups, in particular amino acid amidates or substituted and unsubstituted aryl esters are administered systemically or orally they are capable of hydrolytic cleavage *in vivo* to yield the free acid.

One or more of the acidic hydroxyls are protected. If more than one acidic hydroxyl is protected then the same or a different protecting group is employed, e.g., the esters may be different or the same, or a mixed amidate and ester may be used.

Typical hydroxy protecting groups described in Greene (pages 14-118) include substituted methyl and alkyl ethers, substituted benzyl ethers, silyl ethers, esters including sulfonic acid esters, and carbonates. For example:

- Ethers (methyl, *t*-butyl, allyl);
- Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, *t*-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, *p*-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, *t*-Butoxymethyl, 4-Pentenylloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, Tetrahydrothiopyranyl, 1-Methoxycyclohexyl, 4-Methoxytetrahydropyranyl, 4-Methoxytetrahydrothiopyranyl, 4-Methoxytetrahydrothiopyranyl *S,S*-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-Dioxan-2-yl, Tetrahydrofuranyl, Tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl));
- Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl,
- *p*-Chlorophenyl, *p*-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl);
- Substituted Benzyl Ethers (*p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *p*-Halobenzyl, 2,6-Dichlorobenzyl, *p*-Cyanobenzyl, *p*-Phenylbenzyl, 2- and

- 4-Picolyl, 3-Methyl-2-picolyl *N*-Oxido, Diphenylmethyl, *p,p'*-Dinitrobenzhydryl, 5-Dibenzosuberyl, Triphenylmethyl, α -Naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, Di(*p*-methoxyphenyl)phenylmethyl, Tri(*p*-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyldiphenylmethyl, 4,4',4"-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-Tris(levulinoyloxyphenyl)methyl, 4,4',4"-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4',4"-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzisothiazolyl *S,S*-Dioxido);
- 10 • Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsilyl, Dimethylhexylsilyl, *t*-Butyldimethylsilyl, *t*-Butyldiphenylsilyl, Tribenzylsilyl, Tri-*p*-xylsilyl, Triphenylsilyl, Diphenylmethylsilyl, *t*-Butylmethoxyphenylsilyl);
- 15 • Esters (Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, *p*-Chlorophenoxyacetate, *p*-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, *p*-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate));
- 20 • Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, *p*-Nitrophenyl, Benzyl, *p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *S*-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate);
- 25 • Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, *o*-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate); Miscellaneous Esters (2,6-Dichloro-4-methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3 tetramethylbutyl)phenoxyacetate, 2,4-
- 30 Bis(1,1-dimethylpropyl)phenoxyacetate, Chlorodiphenylacetate, Isobutyrate, Monosuccinate, (*E*)-2-Methyl-2-butenate (Tigloate), *o*-(Methoxycarbonyl)benzoate, *p*-poly-Benzoate, α -Naphthoate, Nitrate, Alkyl *N,N,N',N'*-Tetramethylphosphorodiamidate,

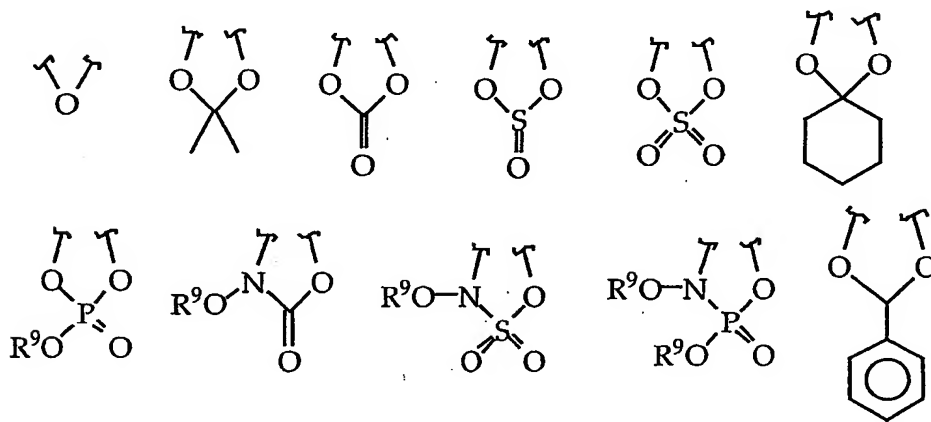
N-Phenylcarbamate, Borate, Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and

- Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzyisulfonate, Tosylate).

Typical 1,2-diol protecting groups (thus, generally where two OH groups are taken together with the protecting functionality) are described in Greene at pages 118-142 and include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-*t*-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene, Cyclohexylidene, Cycloheptylidene, Benzylidene, *p*-Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-Methoxyethylidene, 1-Ethoxyethylidene, 1,2-Dimethoxyethylidene, α -Methoxybenzylidene, 1-(*N,N*-Dimethylamino)ethylidene Derivative, α -(*N,N*-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); Silyl Derivatives (Di-*t*-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropylidisiloxanylidene), and Tetra-*t*-butoxydisiloxane-1,3-diylidene), Cyclic Carbonates, Cyclic Boronates, Ethyl Boronate and Phenyl Boronate.

More typically, 1,2-diol protecting groups include those shown in Table B, still more typically, epoxides, acetonides, cyclic ketals and aryl acetals.

Table B



wherein R^9 is C_1 - C_6 alkyl.

Amino protecting groups

Another set of protecting groups include any of the typical amino protecting groups described by Greene at pages 315-385. They include:

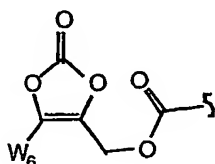
- Carbamates: (methyl and ethyl, 9-fluorenylmethyl, 9(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 4-methoxyphenacyl);
- Substituted Ethyl: (2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-
5 adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(*N,N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidinyl, alkylidithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl,
10 *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl);
- Groups With Assisted Cleavage: (2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-
15 cyanoethyl, *m*-chloro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl);
- Groups Capable of Photolytic Cleavage: (*m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl(*o*-nitrophenyl)methyl); Urea-Type Derivatives (phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, *N'*-
20 phenylaminothiocarbonyl);
- Miscellaneous Carbamates: (*t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-
25 furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, *p*-(*p*'-Methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-
30 trimethylbenzyl);
- Amides: (*N*-formyl, *N*-acetyl, *N*-choroacetyl, *N*-trichloroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridylcarboxamide, *N*-

benzoylphenylalanyl, *N*-benzoyl, *N*-*p*-phenylbenzoyl);

- Amides With Assisted Cleavage: (*N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N'*-dithiobenzyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl)propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, 4,5-diphenyl-3-oxazolin-2-one);
- Cyclic Imide Derivatives: (*N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenylmaleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridonyl);
- *N*-Alkyl and *N*-Aryl Amines: (*N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypentyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, *N*-2-picolylamine *N'*-oxide);
- Imine Derivatives: (*N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenzylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*-(*N'*,*N'*-dimethylaminomethylene, *N*,*N'*-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene);
- Enamine Derivatives: (*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl));
- *N*-Metal Derivatives (*N*-borane derivatives, *N*-diphenylborinic acid derivatives, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, *N*-copper or *N*-zinc chelate);
- *N*-N Derivatives: (*N*-nitro, *N*-nitroso, *N*-oxide);
- *N*-P Derivatives: (*N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, *N*-diphenyl phosphoryl);
- *N*-Si Derivatives, *N*-S Derivatives, and *N*-Sulfonyl Derivatives: (*N*-benzenesulfonyl, *N*-*o*-nitrobenzenesulfonyl, *N*-2,4-dinitrobenzenesulfonyl, *N*-pentachlorobenzenesulfonyl, *N*-2-nitro-4-methoxybenzenesulfonyl, *N*-triphenylmethylsulfonyl, *N*-3-nitropyridinesulfonyl); and *N*-sulfonyl Derivatives (*N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-

4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6-tetramethyl-4-methoxybenzenesulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy-4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*- β -trimethylsilyethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, *N*-phenacysulfonyl).

Protected amino groups include carbamates, amides and amidines, e.g. $-\text{NHC(O)OR}^1$, $-\text{NHC(O)R}^1$ or $-\text{N}=\text{CR}^1\text{N(R}^1)_2$. Another protecting group, also useful as a
 10 prodrug for amino or $-\text{NH(R}^5)$, is:



See for example Alexander, J. et al (1996) *J. Med. Chem.* 39:480-486.

Amino acid and polypeptide protecting group and conjugates

15 An amino acid or polypeptide protecting group of a compound of the invention has the structure $\text{R}^{15}\text{NHCH(R}^{16})\text{C(O)-}$, where R^{15} is H, an amino acid or polypeptide residue, or R^5 , and R^{16} is defined below.

R^{16} is lower alkyl or lower alkyl ($\text{C}_1\text{-C}_6$) substituted with amino, carboxyl, amide, carboxyl ester, hydroxyl, $\text{C}_6\text{-C}_7$ aryl, guanidiny, imidazolyl, indolyl, sulfhydryl, sulfoxide,
 20 and/or alkylphosphate. R^{16} also is taken together with the amino acid $\alpha\text{-N}$ to form a proline residue ($\text{R}^{16} = -\text{CH}_2)_3$). However, R^{16} is generally the side group of a naturally-occurring amino acid such as H, $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{-CH}(\text{CH}_3)_2$, $-\text{CHCH}_3\text{-CH}_2\text{-CH}_3$, $-\text{CH}_2\text{-C}_6\text{H}_5$, $-\text{CH}_2\text{CH}_2\text{-S-CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH(OH)-CH}_3$, $-\text{CH}_2\text{-SH}$, $-\text{CH}_2\text{-C}_6\text{H}_4\text{OH}$, $-\text{CH}_2\text{-CO-NH}_2$, $-\text{CH}_2\text{-CH}_2\text{-CO-NH}_2$, $-\text{CH}_2\text{-COOH}$, $-\text{CH}_2\text{-CH}_2\text{-COOH}$, $-(\text{CH}_2)_4\text{-NH}_2$ and $-(\text{CH}_2)_3\text{-NH-}$
 25 $\text{C(NH}_2)_2\text{-NH}_2$. R^{16} also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

Another set of protecting groups include the residue of an amino-containing compound, in particular an amino acid, a polypeptide, a protecting group, $-\text{NHSO}_2\text{R}$,

NHC(O)R, -N(R)₂, NH₂ or -NH(R)(H), whereby for example a carboxylic acid is reacted, i.e. coupled, with the amine to form an amide, as in C(O)NR₂. A phosphonic acid may be reacted with the amine to form a phosphonamidate, as in -P(O)(OR)(NR₂).

Amino acids have the structure R¹⁷C(O)CH(R¹⁶)NH-, where R¹⁷ is -OH,
5 -OR, an amino acid or a polypeptide residue. Amino acids are low molecular weight compounds, on the order of less than about 1000 MW and which contain at least one amino or imino group and at least one carboxyl group. Generally the amino acids will be found in nature, i.e., can be detected in biological material such as bacteria or other microbes, plants, animals or man. Suitable amino acids typically are alpha amino acids, i.e. compounds
10 characterized by one amino or imino nitrogen atom separated from the carbon atom of one carboxyl group by a single substituted or unsubstituted alpha carbon atom. Of particular interest are hydrophobic residues such as mono- or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues contribute to cell permeability by increasing the partition coefficient of the parental drug. Typically, the residue does not
15 contain a sulfhydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine,
20 glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Additionally, unnatural amino acids, for example, valanine, phenylglycine and homoarginine are also included. Commonly encountered amino acids that are not gene-encoded may also be used in the present invention. All of the amino acids used in the present invention may be either the
25 D- or L- optical isomer. In addition, other peptidomimetics are also useful in the present invention. For a general review, see Spatola, A. F., in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, B. Weinstein, eds., Marcel Dekker, New York, p. 267 (1983).

When protecting groups are single amino acid residues or polypeptides they optionally are substituted at R³ of substituents A¹, A² or A³ in Formula I, or substituted at R₃
30 of substituents A₁, A₂ or A₃ in Formula II. These conjugates are generally produced by forming an amide bond between a carboxyl group of the amino acid (or C-terminal amino acid of a polypeptide for example). Alternatively, conjugates are formed between R³

(Formula I) or R₃ (Formula II) and an amino group of an amino acid or polypeptide.

Generally, only one of any site in the scaffold drug-like compound is amidated with an amino acid as described herein, although it is within the scope of this invention to introduce amino acids at more than one permitted site. Usually, a carboxyl group of R³ is amidated with an amino acid. In general, the α -amino or α -carboxyl group of the amino acid or the terminal amino or carboxyl group of a polypeptide are bonded to the scaffold, parental functionalities. Carboxyl or amino groups in the amino acid side chains generally may be used to form the amide bonds with the parental compound or these groups may need to be protected during synthesis of the conjugates as described further below.

With respect to the carboxyl-containing side chains of amino acids or polypeptides it will be understood that the carboxyl group optionally will be blocked, e.g. by R¹, esterified with R⁵ or amidated. Similarly, the amino side chains R¹⁶ optionally will be blocked with R¹ or substituted with R⁵.

Such ester or amide bonds with side chain amino or carboxyl groups, like the esters or amides with the parental molecule, optionally are hydrolyzable *in vivo* or *in vitro* under acidic (pH <3) or basic (pH >10) conditions. Alternatively, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular environments. The esters or amino acid or polypeptide amidates also are useful as intermediates for the preparation of the parental molecule containing free amino or carboxyl groups. The free acid or base of the parental compound, for example, is readily formed from the esters or amino acid or polypeptide conjugates of this invention by conventional hydrolysis procedures.

When an amino acid residue contains one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or mixtures thereof may be used. In general, if the intermediates are to be hydrolyzed non-enzymatically (as would be the case where the amides are used as chemical intermediates for the free acids or free amines), D isomers are useful. On the other hand, L isomers are more versatile since they can be susceptible to both non-enzymatic and enzymatic hydrolysis, and are more efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acids whose residues are represented by R^x or R^y include the following:

Glycine;

- Aminopolycarboxylic acids, e.g., aspartic acid, β -hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β -methyiaspartic acid, β -methylglutamic acid, β , β -dimethyiaspartic acid, γ -hydroxyglutamic acid, β , γ -dihydroxyglutamic acid, β -phenylglutamic acid, γ -methyleneglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and
- 5 2-aminosebacic acid;
- Amino acid amides such as glutamine and asparagine;
- Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyric acid, ornithine, citrulline, homoarginine, homocitrulline, hydroxylysine, allohydroxylysine and diaminobutyric acid;
- 10 Other basic amino acid residues such as histidine;
- Diaminodicarboxylic acids such as α , α' -diaminosuccinic acid, α , α' -diaminoglutaric acid, α , α' -diaminoadipic acid, α , α' -diaminopimelic acid, α , α' -diamino- β -hydroxypimelic acid, α , α' -diaminosuberic acid, α , α' -diaminoazelaic acid, and α , α' -diaminosebacic acid;
- Imino acids such as proline, hydroxyproline, allohydroxyproline, γ -methylproline,
- 15 pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid;
- A mono- or di-alkyl (typically C₁-C₈ branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyric acid, norvaline, norleucine, heptyline, α -methylserine, α -amino- α -methyl- γ -hydroxyvaleric acid, α -amino- α -methyl- δ -hydroxyvaleric acid, α -amino- α -methyl- ϵ -hydroxycaproic acid, isovaline, α -methylglutamic acid, α -aminoisobutyric acid,
- 20 α -aminodiethylacetic acid, α -aminodiisopropylacetic acid, α -aminodi-n-propylacetic acid, α -aminodiisobutylacetic acid, α -aminodi-n-butylacetic acid, α -aminoethylisopropylacetic acid, α -amino-n-propylacetic acid, α -aminodiisobutyric acid, α -methylaspartic acid, α -methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid, isoleucine, allose, *tert*-leucine, β -methyltryptophan and α -amino- β -ethyl- β -phenylpropionic acid;
- 25 β -phenylserine;
- Aliphatic α -amino- β -hydroxy acids such as serine, β -hydroxyisoleucine, β -hydroxynorleucine, β -hydroxynorvaline, and α -amino- β -hydroxystearic acid;
- α -Amino, α -, γ -, δ - or ϵ -hydroxy acids such as homoserine, δ -hydroxynorvaline, γ -hydroxynorvaline and ϵ -hydroxynorleucine residues; canavine and canaline; γ -
- 30 hydroxyornithine;
- 2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid;
- α -Amino- β -thiols such as penicillamine, β -thiolnorvaline or β -thiolbutyric acid;

Other sulfur containing amino acid residues including cysteine; homocystine, β -phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocystine;

Phenylalanine, tryptophan and ring-substituted α -amino acids such as the phenyl- or
5 cyclohexylamino acids α -aminophenylacetic acid, α -aminocyclohexylacetic acid and α -
amino- β -cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl,
lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g.,
tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dichloro, o-, m- or p-methyl-, 2,4,6-
trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitro-phenylalanine); furyl-, thienyl-,
10 pyridyl-, pyrimidinyl-, purinyl- or naphthyl-alanines; and tryptophan analogues and
derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-
carboxytryptophan;

α -Amino substituted amino acids including sarcosine (N-methylglycine), N-
benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-
15 benzylphenylalanine, N-methylvaline and N-benzylvaline; and

α -Hydroxy and substituted α -hydroxy amino acids including serine, threonine,
allothreonine, phosphoserine and phosphothreonine.

Polypeptides are polymers of amino acids in which a carboxyl group of one amino
acid monomer is bonded to an amino or imino group of the next amino acid monomer by an
20 amide bond. Polypeptides include dipeptides, low molecular weight polypeptides (about
1500-5000 MW) and proteins. Proteins optionally contain 3, 5, 10, 50, 75, 100 or more
residues, and suitably are substantially sequence-homologous with human, animal, plant or
microbial proteins. They include enzymes (e.g., hydrogen peroxidase) as well as
immunogens such as KLH, or antibodies or proteins of any type against which one wishes to
25 raise an immune response. The nature and identity of the polypeptide may vary widely.

The polypeptide amidates are useful as immunogens in raising antibodies against
either the polypeptide (if it is not immunogenic in the animal to which it is administered) or
against the epitopes on the remainder of the compound of this invention.

Antibodies capable of binding to the parental non-peptidyl compound are used to
30 separate the parental compound from mixtures, for example in diagnosis or manufacturing of
the parental compound. The conjugates of parental compound and polypeptide generally are
more immunogenic than the polypeptides in closely homologous animals, and therefore make

the polypeptide more immunogenic for facilitating raising antibodies against it. Accordingly, the polypeptide or protein may be immunogenic in an animal typically used to raise antibodies, e.g., rabbit, mouse, horse, or rat. The polypeptide optionally contains a peptidolytic enzyme cleavage site at the peptide bond between the first and second residues adjacent to the acidic heteroatom. Such cleavage sites are flanked by enzymatic recognition structures, e.g. a particular sequence of residues recognized by a peptidolytic enzyme.

Peptidolytic enzymes for cleaving the polypeptide conjugates of this invention are well known, and in particular include carboxypeptidases, which digest polypeptides by removing C-terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a dipeptide (having a given pair of residues and a free carboxyl terminus) is covalently bonded through its α -amino group to the phosphorus or carbon atoms of the compounds herein. In certain embodiments, a phosphonate group substituted with an amino acid or peptide will be cleaved by the appropriate peptidolytic enzyme, leaving the carboxyl of the proximal amino acid residue to autocatalytically cleave the phosphonoamidate bond.

Suitable dipeptidyl groups (designated by their single letter code) are AA, AR, AN, AD, AC, AE, AQ, AG, AH, AI, AL, AK, AM, AF, AP, AS, AT, AW, AY, AV, RA, RR, RN, RD, RC, RE, RQ, RG, RH, RI, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NR, NN, ND, NC, NE, NQ, NG, NH, NI, NL, NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH, DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN, ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY, GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HI, HL, HK, HM, HF, HP, HS, HT, HW, HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS, IT, IW, IY, IV, LA, LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR, KN, KD, KC, KE, KQ, KG, KH, KI, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA, MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY, MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV, PA, PR, PN, PD, PC, PE, PQ, PG, PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA, SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, SM, SF, SP, SS, ST, SW, SY, SV, TA, TR, TN,

TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR, WN,
 WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY, WV,
 YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT, YW, YY,
 YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, VS, VT, VW, VY
 5 and VV.

Tripeptide residues are also useful as protecting groups. When a phosphonate is to be protected, the sequence $-X^4\text{-pro-X}^5-$ (where X^4 is any amino acid residue and X^5 is an amino acid residue, a carboxyl ester of proline, or hydrogen) will be cleaved by luminal carboxypeptidase to yield X^4 with a free carboxyl, which in turn is expected to
 10 autocatalytically cleave the phosphonoamidate bond. The carboxy group of X^5 optionally is esterified with benzyl.

Dipeptide or tripeptide species can be selected on the basis of known transport properties and/or susceptibility to peptidases that can affect transport to intestinal mucosal or other cell types. Dipeptides and tripeptides lacking an α -amino group are transport substrates
 15 for the peptide transporter found in brush border membrane of intestinal mucosal cells (Bai, J.P.F., (1992) *Pharm Res.* 9:969-978. Transport competent peptides can thus be used to enhance bioavailability of the amidate compounds. Di- or tripeptides having one or more amino acids in the D configuration may be compatible with peptide transport. Amino acids in the D configuration can be used to reduce the susceptibility of a di- or tripeptide to
 20 hydrolysis by proteases common to the brush border such as aminopeptidase N. In addition, di- or tripeptides alternatively are selected on the basis of their relative resistance to hydrolysis by proteases found in the lumen of the intestine. For example, tripeptides or polypeptides lacking asp and/or glu are poor substrates for aminopeptidase A, di- or tripeptides lacking amino acid residues on the N-terminal side of hydrophobic amino acids
 25 (leu, tyr, phe, val, trp) are poor substrates for endopeptidase, and peptides lacking a pro residue at the penultimate position at a free carboxyl terminus are poor substrates for carboxypeptidase P. Similar considerations can also be applied to the selection of peptides that are either relatively resistant or relatively susceptible to hydrolysis by cytosolic, renal, hepatic, serum or other peptidases. Such poorly cleaved polypeptide amidates are
 30 immunogens or are useful for bonding to proteins in order to prepare immunogens.

Phosphonate analogs of known experimental or approved Protease Inhibitor Drugs

The known experimental or approved protease inhibitor drugs which can be derivatized in accord with the present invention must contain at least one functional group capable of linking, i.e. bonding to the phosphorus atom in the phosphonate moiety. The phosphonate derivatives of Formulas I-VIII may cleave *in vivo* in stages after they have reached the desired site of action, i.e. inside a cell. One mechanism of action inside a cell may entail a first cleavage, e.g. by esterase, to provide a negatively-charged "locked-in" intermediate. Cleavage of a terminal ester grouping in Formulas I-VIII thus affords an unstable intermediate which releases a negatively charged "locked in" intermediate.

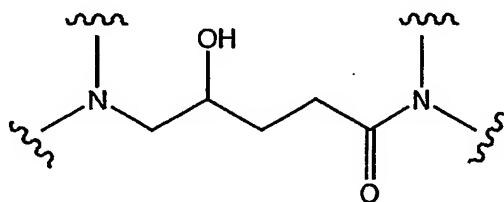
After passage inside a cell, intracellular enzymatic cleavage or modification of the phosphonate prodrug compound may result in an intracellular accumulation of the cleaved or modified compound by a "trapping" mechanism. The cleaved or modified compound may then be "locked-in" the cell, i.e. accumulate in the cell by a significant change in charge, polarity, or other physical property change which decreases the rate at which the cleaved or modified compound can exit the cell, relative to the rate at which it entered as the phosphonate prodrug. Other mechanisms by which a therapeutic effect is achieved may be operative as well. Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases.

In selected instances in which the drug is of the nucleoside type, such as is the case of zidovudine and numerous other antiretroviral agents, it is known that the drug is activated *in vivo* by phosphorylation. Such activation may occur in the present system by enzymatic conversion of the "locked-in" intermediate with phosphokinase to the active phosphonate diphosphate and/or by phosphorylation of the drug itself after its release from the "locked-in" intermediate as described above. In either case, the original nucleoside-type drug will be converted, via the derivatives of this invention, to the active phosphorylated species.

From the foregoing, it will be apparent that many structurally different known approved and experimental HIV protease inhibitor drugs can be derivatized in accord with the present invention. Numerous such drugs are specifically mentioned herein. However, it should be understood that the discussion of drug families and their specific members for derivatization according to this invention is not intended to be exhaustive, but merely illustrative.

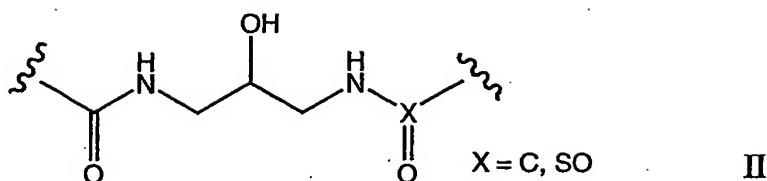
As another example, when the selected drug contains multiple reactive hydroxyl functions, a mixture of intermediates and final products may again be obtained. In the unusual case in which all hydroxy groups are approximately equally reactive, there is not expected to be a single, predominant product, as each mono-substituted product will be
 5 obtained in approximate by equal amounts, while a lesser amount of multiply-substituted product will also result. Generally speaking, however, one of the hydroxyl groups will be more susceptible to substitution than the other(s), e.g. a primary hydroxyl will be more reactive than a secondary hydroxyl, an unhindered hydroxyl will be more reactive than a hindered one. Consequently, the major product will be a mono-substituted one in which the
 10 most reactive hydroxyl has been derivatized while other mono-substituted and multiply-substituted products may be obtained as minor products.

Formula I compounds having a 3-hydroxy-5-amino-pentamide core include Indinavir-like phosphonate protease inhibitors (ILPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 3-hydroxy-5-amino-pentamide
 15 core which have been identified as CGP-49689, CGP-53437, CGP-57813 (Novartis); L-689502, L-693549, L-748496, L-754394, MK-944a, Iddb63, Iddb88 (Merck); Lasinavir (Bristol-Myers Squibb); U-81749 (PNU/Pfizer); SB-203386, SKF-108922 (SmithKline Beecham).

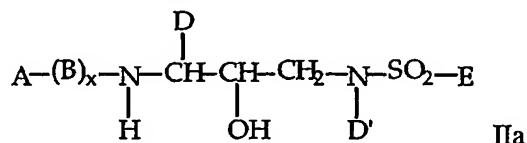


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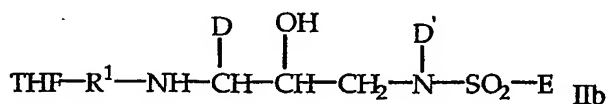
Formula II compounds having a 2-hydroxy-1, 3-amino-propylamide or 2-hydroxy-1,3-amino-propylaminosulfone core include Amprenavir-like phosphonate protease inhibitors (AMLPPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 2-hydroxy-3-amido-propylamide or 2-hydroxy-3-amido-propylaminosulfone core which have been identified as Droxinavir, Telinavir, Iddb51
 20 (Searle); Ph4556 (WO 95/29922; Ph5145 (WO 96/31527; DPC-681, DPC-684 (DuPont); VB-11328 (Vertex); TMC-114 (Tibotech/Johnson & Johnson). Formula II compounds also include phosphonate analogs of fosamprenavir where the 2-hydroxy is phosphorylated, i.e. having a or 2-phosphate-1,3-amino-propylaminosulfone core (US Patent No. 6,436,989).



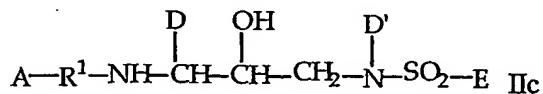
The embodiments of the invention also include the following phosphonate analogs of Formula II, represented as Formulas IIa-Ig:



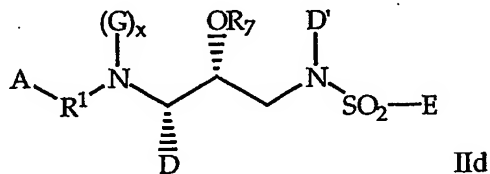
described as "(I)" in: WO 94/05639 (published 17 March 1994) at page 4, line 15, to page 6, line 27, page 15, line 21, to page 17, line 33, and Claim 1; US Patent No. 5,585,397 (issued 17 December 1996) at col. 2, line 45, to col. 3, line 53, and col. 8, line 1, to col. 9, line 12; US Patent No. 5,783,701 (issued 21 July 1998) at col. 2, line 43, to col. 3, line 64, col. 8, line 13, to col. 9, line 33, and Claim 1; US Patent No. 5,856,353 (issued 5 January 1999) at col. 2, line 45, to col. 3, line 65, col. 8, line 14, to col. 9, line 37, and Claim 1; US Patent No. 5,977,137 (issued 2 November 1999) at col. 2, line 43, to col. 3, line 65, col. 8, line 15, to col. 9, line 38, and Claim 1; and US Patent No. 6,004,957 (issued 21 December 1999) at col. 2, line 47, to col. 4, line 3, col. 8, line 18, to col. 9, line 41, and Claim 1 therein.



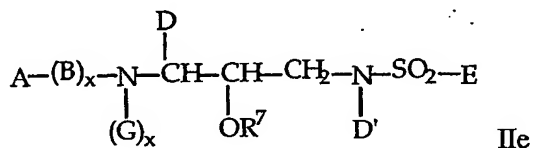
described as "(I)" in: WO 96/33184 (published 24 October 1996) at page 4, line 19, to page 6, line 5, page 17, line 11, to page 19, line 31, and Claim 1; and US Patent No. 5,723,490 (issued 3 March 1998) at col. 2, line 49, to col. 3, line 39, col. 8, line 66, to col. 10, line 36, and Claim 1.



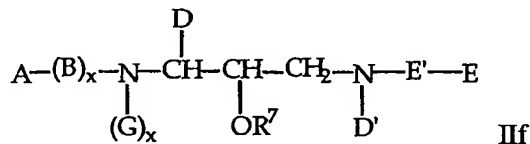
described as "(I)" in: WO 96/33187 (published 24 October 1996) at page 4, line 23, to page 6, line 18, page 18, line 8, to page 21, line 18, and Claims 1 and 6; US Patent No. 5,691,372 (issued 25 November 1997) at col. 2, line 43, to col. 3, line 47, col. 9, line 21, to col. 11, line 5, and Claims 1 and 5; and US Patent No. 5,990,155 (issued 23 November 1999) at col. 2, line 46, to col. 3, line 55, col. 9, line 25, to col. 11, line 13, and Claims 1 and 3.



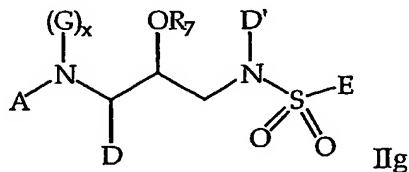
described as "(I)" in: WO 99/33793 (published 8 July 1999) at page 4, line 1, to page 7, line 29, page 17, line 1, to page 20, line 33, and Claim 1.



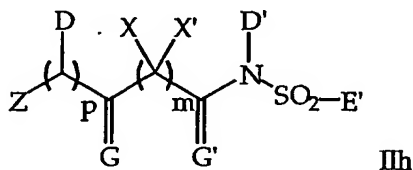
described as "(I)" in: WO 99/33815 (published 8 July 1999) at page 4, line 1, to page 7, line 19, page 12, line 18, to page 16, line 7, and Claim 1; and WO 99/65870 (published 23 December 1999) at page 4, line 7, to page 8, line 4, page 12, line 7, to page 16, line 4, and Claim 1.



described as "(I)" in: WO 00/47551 (published 17 August 2000) at page 4, line 10, to page 8, line 29, page 13, line 14, to page 17, line 32, and Claim 1.

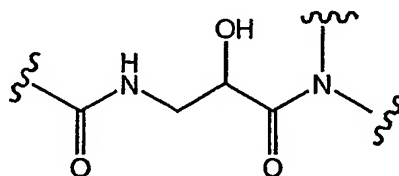


described as "(I)" in: WO 00/76961 (published 21 December 2000) at page 5, line 1, to page 10, line 24, page 14, line 28, to page 20, line 21, and Claim 1.

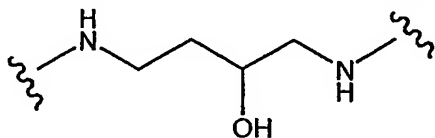


described as "(I)" in: WO 99/33792 (published 8 July 1999) at page 4, line 5, to page 7, line 35, page 17, line 10, to page 21, line 6, and Claim 1; WO 95/24385 (published 14 September 1995) at page 4, line 24, to page 7, line 14, page 16, line 20, to page 19, line 8, and Claims 1 and 29; and US Patent No. 6,127,372 (issued 3 October 2000) at col. 2, line 58, to col. 4, line 28, col. 8, line 66, to col. 10, line 37, and Claim 1.

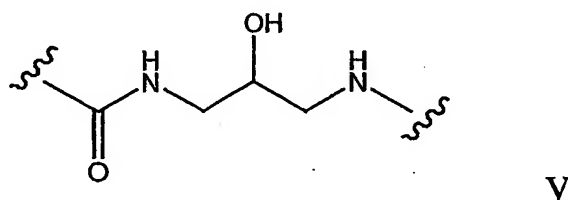
Formula III compounds having a 2-hydroxy-3-amino-propylamide core include KNI-like phosphonate protease inhibitors (KNILPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 2-hydroxy-3-amido-propylamide or 2-hydroxy-3-amido-propylaminosulfone core which have been identified as KNI-764 (JE-2147, AG1776); KNI-102, KNI-227, KNI-241, KNI-272, KNI-413, KNI-549, KNI-577, KNI-727, JE-2178 (Japan Energy); Ph3939 (EP 587311); R-87366, Iddb134 (Sankyo); VLE-776 (Scripps Institute).



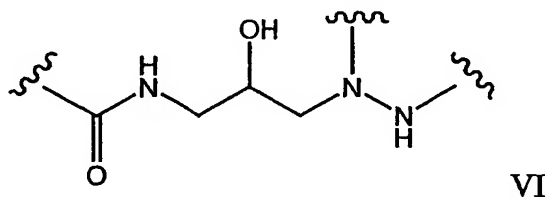
Formula IV compounds having a 2-hydroxy-4-amino-butylamine core include Ritonavir-like phosphonate protease inhibitors (RLPPI) and Lopinavir-like phosphonate protease inhibitors (LLPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 2-hydroxy-4-amino-butylamine core which have been identified as A-76928, A-80735, A-80987 (Abbott Laboratories).



Formula V compounds having an acylated 1,3-diaminopropane core include Saquinavir-like phosphonate protease inhibitors (SLPPI) and Nelfinavir-like phosphonate protease inhibitors (NLPPI). Compounds of the invention include phosphonate analogs of
5 other known PI compounds with an acylated 1,3-diaminopropane core which have been identified as Ro-33-2910, Ro-33-4649 (Hofman La Roche); BMS-182193, BMS-186318, BMS-187071 (Bristol-Myers Squibb); JG-365 (Univ. of Wisconsin); L-704325, L-738872, L-739594, L-743770 (Merck & Co.); LB-71206 (LG Chemical Ltd.); LY-296242, LY-314163, LY-316683, LY-326620 (Eli Lilly Co.), Palinavir (BioMega/BI); Ph5640, Ph6090 (WO
10 97/21100).

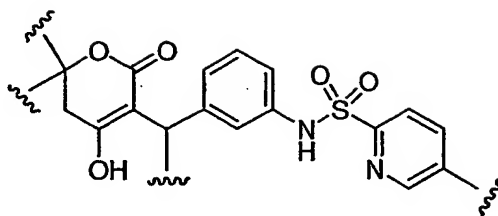


Formula VI compounds having a 2-hydroxy-3-diaza-propylamide core include Atazanavir-like phosphonate protease inhibitors (ATLPPI). Compounds of the invention
15 include phosphonate analogs of other known PI compounds with a 2-hydroxy-3-diaza-propylamide core which have been identified as CGP-56603, CGP-53820, CGP-70726 (Novartis), ABT-538 (Abbott Laboratories), and DG-35 (National Cancer Institute).



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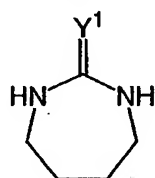
Formula VII compounds having sulfonamide 5,6-dihydro-4-hydroxy-2-pyrene core include Tipranavir-like phosphonate protease inhibitors (TLPPI).



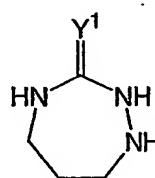
VII

Formula VIII compounds have a six or seven-membered ring, cyclic carbonyl, sulfone, or sulfonyl core, where Y^1 is oxygen, sulfur, or substituted nitrogen and $M2$ is 1 or 2. The invention includes Cyclic carbonyl-like phosphonate protease inhibitor compounds

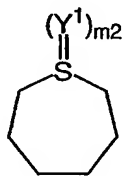
5 (CCLPPI), e.g. Formula VIIIa-d.



VIIIa

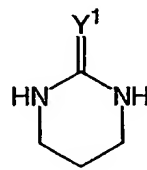


VIIIb



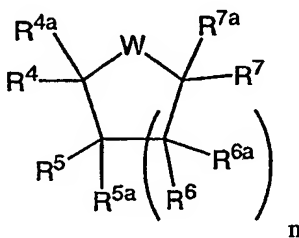
VIIIc

and



VIIIId;

10 Cyclic carbonyl protease inhibitors without a phosphonate group are described in US Patent Nos. RE37781; 6,503,898; 5,880,295; 5,811,422; 5,610,294; 5,559,252; and 5,506,355, as well as patent applications and granted patents which are equivalents of, or related by priority claims thereto. CCLPPI compounds also include phosphonate analogs of:



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described as "(I)" in WO 94/19329 (published 1 September 1994) at page 4, line 23, to page 21, line 16 and Claim 1. Also contemplated are patent applications and granted patents which are equivalents of or related by priority claims to WO 94/19329.

20 Stereoisomers

The compounds of the invention, exemplified by Formula I and II, may have chiral centers, e.g. chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The compounds of the invention can also exist as tautomeric isomers in certain cases. All though only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Salts and Hydrates

The compositions of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+ , Li^+ , K^+ , Ca^{+2} and Mg^{+2} . Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+ , Na^+ , and K^+ . A less soluble metal salt may be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic

acids, e.g., HCl, HBr, H₂SO₄, H₃PO₄ or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

5 Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any of the amino acids described above are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine,
10 alanine, isoleucine, or leucine.

Methods of Inhibition of HIV Protease

Another aspect of the invention relates to methods of inhibiting the activity of HIV protease comprising the step of treating a sample suspected of containing HIV with a composition of the invention.

15 Compositions of the invention may act as inhibitors of HIV protease, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of HIV protease having a geometry unique to HIV protease. Compositions binding HIV protease may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this
20 method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of HIV protease. Accordingly, the invention relates to methods of detecting HIV protease in a sample suspected of containing HIV protease comprising the steps of: treating a sample suspected of containing HIV protease with a composition comprising a compound of the invention bound to a label; and observing the
25 effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl, carboxyl, sulfhydryl or amino.

30 Within the context of the invention, samples suspected of containing HIV protease include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal

fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces HIV protease, frequently a pathogenic organism such as HIV. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of HIV protease after application of the composition can be observed by any method including direct and indirect methods of detecting HIV protease activity. Quantitative, qualitative, and semiquantitative methods of determining HIV protease activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain HIV protease include the HIV virus. The compounds of this invention are useful in the treatment or prophylaxis of HIV infections in animals or in man.

However, in screening compounds capable of inhibiting human immunodeficiency viruses, it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

Screens for HIV protease Inhibitors.

Compositions of the invention are screened for inhibitory activity against HIV protease by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of HIV protease *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro* K_i (inhibitory constants) of less than about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for *in vivo* use.

Useful *in vitro* screens have been described in detail and will not be elaborated here. However, the examples describe suitable *in vitro* assays.

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextran, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded
5 tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For infections of the eye or other external tissues e.g. mouth and skin, the
10 formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-
15 miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol
20 (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known
25 ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make
30 up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween[®] 60, Span[®] 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the
5 desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters
10 known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise a
15 combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules,
20 syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic
25 pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated
30 or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a

longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or
5 kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl
10 methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g.,
heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester
15 derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable
20 oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

25 Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be
30 present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a

mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μ g of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such

formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10%, and particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; 5 pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

10 Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns, such as 0.5, 1, 30, 35 etc., which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder 15 administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of HIV infections as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the 20 active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening 25 agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared 30 from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

5 The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These
10 veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled
15 and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical formulation,
20 and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg
25 body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes
30 include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the

condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy

Compositions of the invention are also used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating viral infections the compositions of the invention may be combined with other antivirals such as other protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors or HIV integrase inhibitors.

It is possible to combine any compound of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to an HIV infected patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. Second and third active ingredients in the combination may have anti-HIV activity. Exemplary active ingredients to be administered in combination with compounds of the invention are protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and HIV integrase inhibitors.

The combination therapy may provide "synergy" and "synergistic", i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g. in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. ^{14}C or ^3H) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no HIV protease inhibitory activity of their own.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37°C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The phosphonate prodrugs of the invention typically will be stable in the digestive system but may be substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

Exemplary Methods of Making the Compounds of the Invention.

The invention provides many methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art, such as those elaborated in "Compendium of Organic Synthetic Methods" (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and

Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., "Advanced Organic Chemistry, Third Edition", (John Wiley & Sons, New York, 1985), "Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes", Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

Dialkyl phosphonates may be prepared according to the methods of: Quast et al (1974) *Synthesis* 490; Stowell et al (1990) *Tetrahedron Lett.* 3261; US Patent No. 5,663,159.

In general, synthesis of phosphonate esters is achieved by coupling a nucleophile amine or alcohol with the corresponding activated phosphonate electrophilic precursor. For example, chlorophosphonate addition on to 5'-hydroxy of nucleoside is a well known method for preparation of nucleoside phosphate monoesters. The activated precursor can be prepared by several well known methods. Chlorophosphonates useful for synthesis of the prodrugs are prepared from the substituted-1,3-propanediol (Wissner, et al, (1992) *J. Med Chem.* 35:1650). Chlorophosphonates are made by oxidation of the corresponding chlorophospholanes (Anderson, et al, (1984) *J. Org. Chem.* 49:1304) which are obtained by reaction of the substituted diol with phosphorus trichloride. Alternatively, the chlorophosphonate agent is made by treating substituted-1,3-diols with phosphorusoxychloride (Patois, et al, (1990) *J. Chem. Soc. Perkin Trans. I*, 1577). Chlorophosphonate species may also be generated in situ from corresponding cyclic phosphites (Silverburg, et al., (1996) *Tetrahedron Lett.*, 37:771-774), which in turn can be either made from chlorophospholane or phosphoramidate intermediate. Phosphorofluoridate intermediate prepared either from pyrophosphate or phosphoric acid may also act as precursor in preparation of cyclic prodrugs (Watanabe et al., (1988) *Tetrahedron Lett.*, 29:5763-66). Caution: fluorophosphonate compounds may be highly toxic!

Phosphonate prodrugs of the present invention may also be prepared from the precursor free acid by Mitsunobu reactions (Mitsunobu, (1981) *Synthesis*, 1; Campbell, (1992) *J. Org. Chem.*, 52:6331), and other acid coupling reagents including, but not limited to, carbodiimides (Alexander, et al, (1994) *Collect. Czech. Chem. Commun.* 59:1853; Casara, et al, (1992) *Bioorg. Med. Chem. Lett.*, 2:145; Ohashi, et al, (1988) *Tetrahedron Lett.*, 29:1189), and benzotriazolyloxytris-(dimethylamino)phosphonium salts (Campagne, et al, (1993) *Tetrahedron Lett.*, 34:6743).

Aryl halides undergo Ni^{+2} catalyzed reaction with phosphite derivatives to give aryl phosphonate containing compounds (Balthazar, et al (1980) *J. Org. Chem.* 45:5425). Phosphonates may also be prepared from the chlorophosphonate in the presence of a palladium catalyst using aromatic triflates (Petrakis, et al, (1987) *J. Am. Chem. Soc.* 109:2831; 5 Lu, et al, (1987) *Synthesis*, 726). In another method, aryl phosphonate esters are prepared from aryl phosphates under anionic rearrangement conditions (Melvin (1981) *Tetrahedron Lett.* 22:3375; Casteel, et al, (1991) *Synthesis*, 691). N-Alkoxy aryl salts with alkali metal derivatives of cyclic alkyl phosphonate provide general synthesis for heteroaryl-2-phosphonate linkers (Redmore (1970) *J. Org. Chem.* 35:4114). These above mentioned 10 methods can also be extended to compounds where the W^5 group is a heterocycle. Cyclic-1,3-propanyl prodrugs of phosphonates are also synthesized from phosphonic diacids and substituted propane-1,3-diols using a coupling reagent such as 1,3-dicyclohexylcarbodiimide (DCC) in presence of a base (e.g., pyridine). Other carbodiimide based coupling agents like 1,3-disopropylcarbodiimide or water soluble reagent, 1-(3-dimethylaminopropyl)-3- 15 ethylcarbodiimide hydrochloride (EDCI) can also be utilized for the synthesis of cyclic phosphonate prodrugs.

The carbamoyl group may be formed by reaction of a hydroxy group according to the methods known in the art, including the teachings of Ellis, US 2002/0103378 A1 and Hajima, US Patent No. 6,018,049.

20 Schemes and Examples

A number of exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods.

General aspects of these exemplary methods are described below and in the 25 Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains 30 detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C , solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a

water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either
5 protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

10 Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g. inert gas environments) are common in the art and will be applied when applicable.

The terms "treated", "treating", "treatment", and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for
15 indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that
20 compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents,
25 pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to
30 successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes above and in the examples (hereafter

"exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction
5 products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods
10 including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent
15 selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as
20 crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply
25 techniques most likely to achieve the desired separation.

A single stereoisomer, e.g. an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*,
30 113:(3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2)

formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically
5 pure chiral bases such as brucine, quinine, ephedrine, strychnine, α -methyl- β -phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such
10 as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric
15 compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g. (-) menthyl chloroformate in the presence of base, or Mosher ester, α -methoxy- α -
20 (trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic
25 mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

30 All literature and patent citations above are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described

in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following Embodiments. It is apparent that certain modifications of the methods and compositions of the following Embodiments can be made within the scope and spirit of the invention.

5 Examples General Section

The following Examples refer to the Schemes.

Some Examples have been performed multiple times. In repeated Examples, reaction conditions such as time, temperature, concentration and the like, and yields were within normal experimental ranges. In repeated Examples where significant modifications were made, these have been noted where the results varied significantly from those described. In 10 Examples where different starting materials were used, these are noted. When the repeated Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl ester", this intends that an otherwise present group, in this case typically a methyl ester, is taken to be the same group modified as indicated.

15

In a number of the following schemes, the term "etc" appears as a substituent on chemical structures and as a term within the schemes. When used in the charts, the term is defined for each chart. When the term "etc" appears in a scheme and is not a substituent on a chemical structure, it means "and the like".

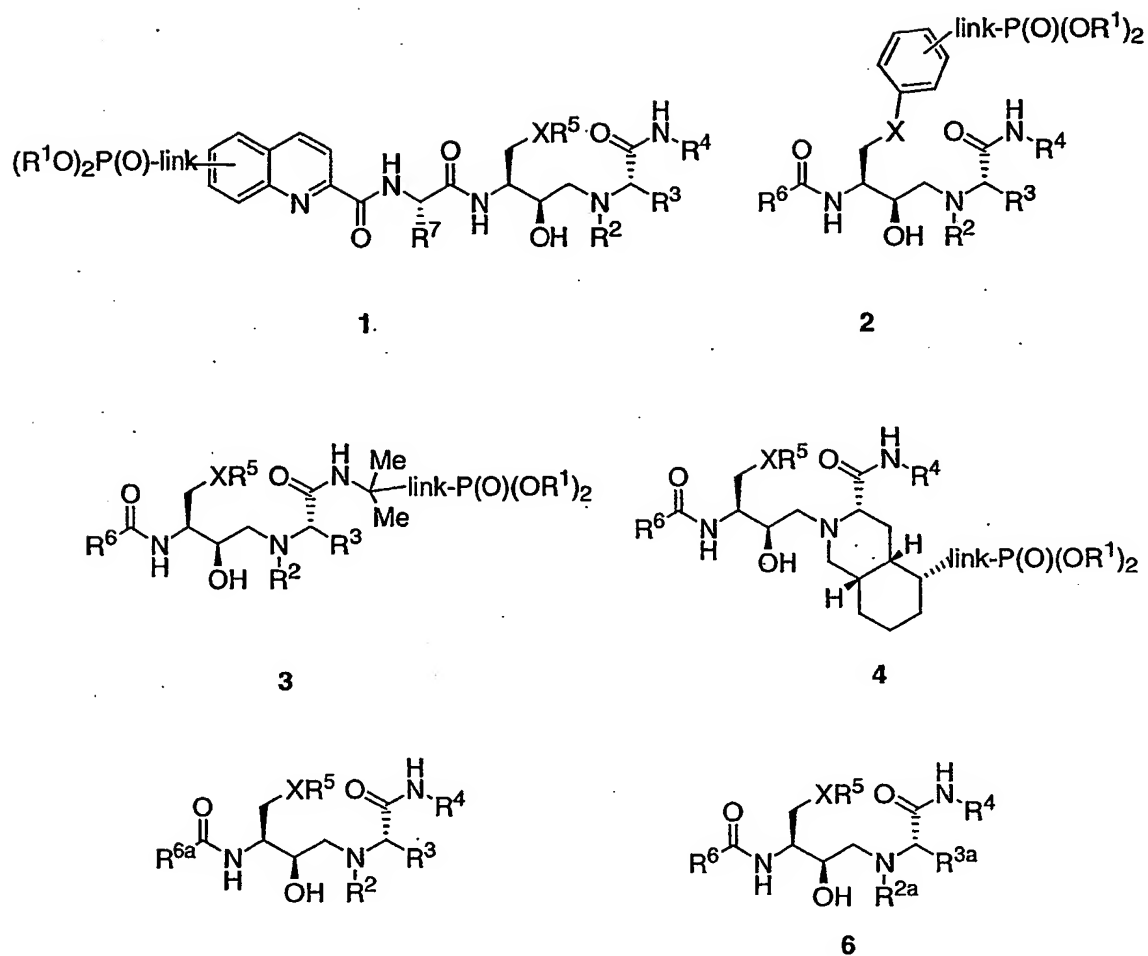
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Saquinavir-like phosphonate protease inhibitors (SLPPI)

Preparation of the intermediate phosphonate esters.

- 10 The structures of the intermediate phosphonate esters 1 to 6, and the structures for the component groups R^1 , R^4 and R^7 of this invention are shown in Chart 1.
- The structures of the $R^2NHCH(R^3)CONHR^4$ and R^5XCH_2 components are shown in Charts 2 and 2a, and the structures of the R^6COOH components are shown in Charts 3a, 3b and 3c.
- Specific stereoisomers of some of the structures are shown in Charts 1, 2 and 3; however, all
- 15 stereoisomers are utilized in the syntheses of the compounds 1 to 6. Subsequent chemical modifications to the compounds 1 to 6, as described herein, permit the synthesis of the final compounds of this invention.
- The intermediate compounds 1 to 6 incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached
- 20 structures. Charts 4 and 5 illustrate examples of the linking groups present in the structures 1 – 5, and in which "etc" refers to the scaffold, e.g., saquinavir.

Chart 1'



R^{6a} = phosphonate-containing R^6

R^{2a} , R^{3a} = phosphonate-containing R^2 or R^3

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^4 = $\text{CH}(\text{CH}_3)_3$; CH_2CF_3 ; $\text{CH}_2\text{C}_6\text{H}_4(\text{CH}_3)_2$

R^7 = alkyl, $\text{CH}_2\text{SO}_2\text{CH}_3$, $\text{C}(\text{CH}_3)_2\text{SO}_2\text{CH}_3$, CH_2CONH_2 , CH_2SCH_3 , imidaz-4-ylmethyl, CH_2NHAc , $\text{CH}_2\text{NHCOCF}_3$

X = S, direct bond

Chart 2

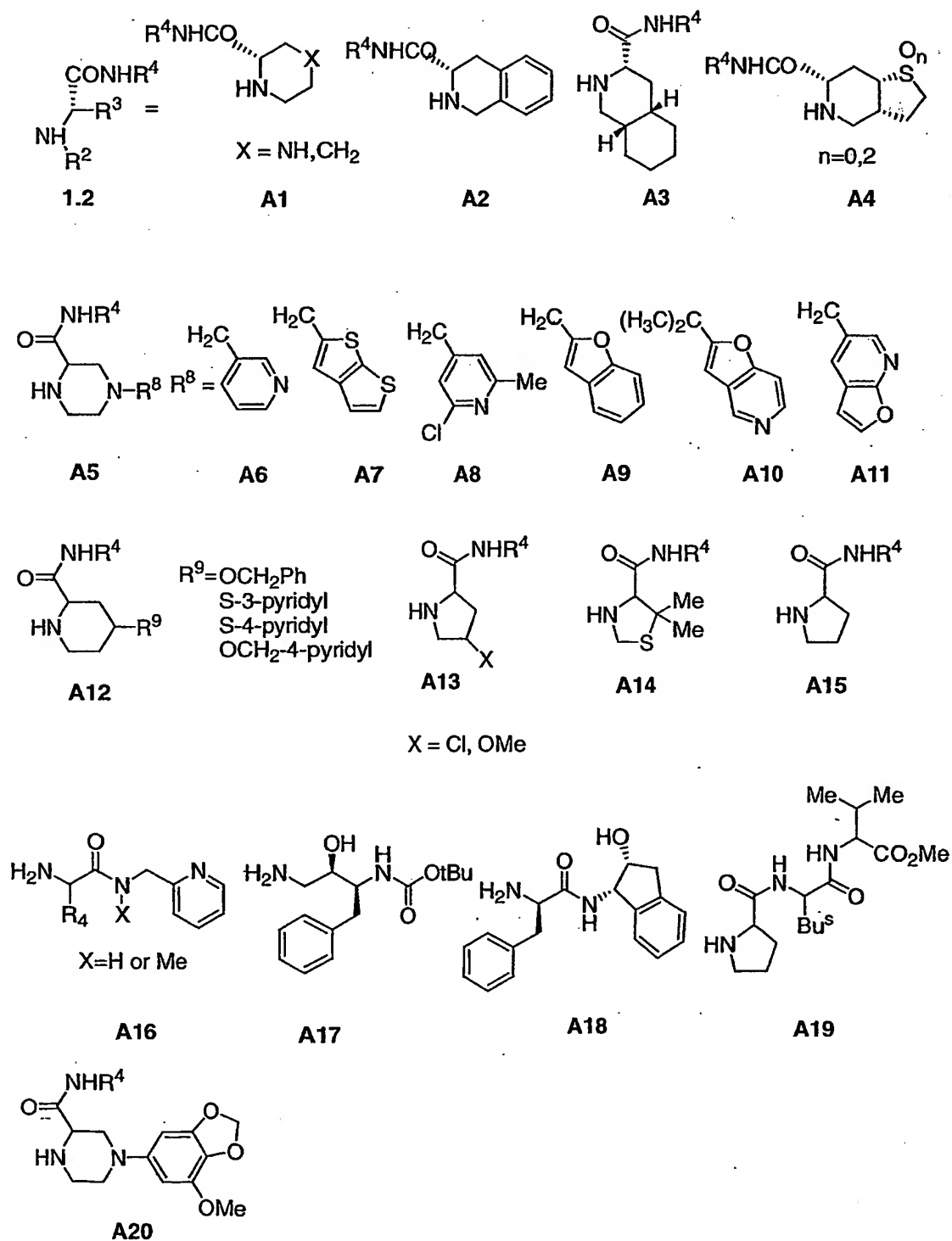
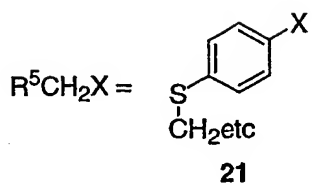
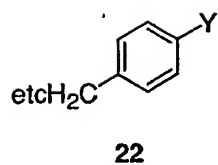


Chart 2a



X = H, F



Y = H, OC₂H₅, OCH₂C₆H₅

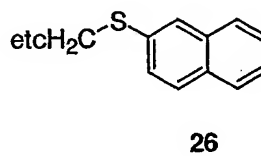
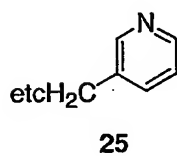
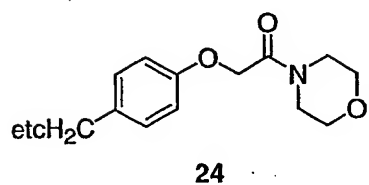
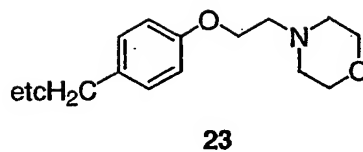
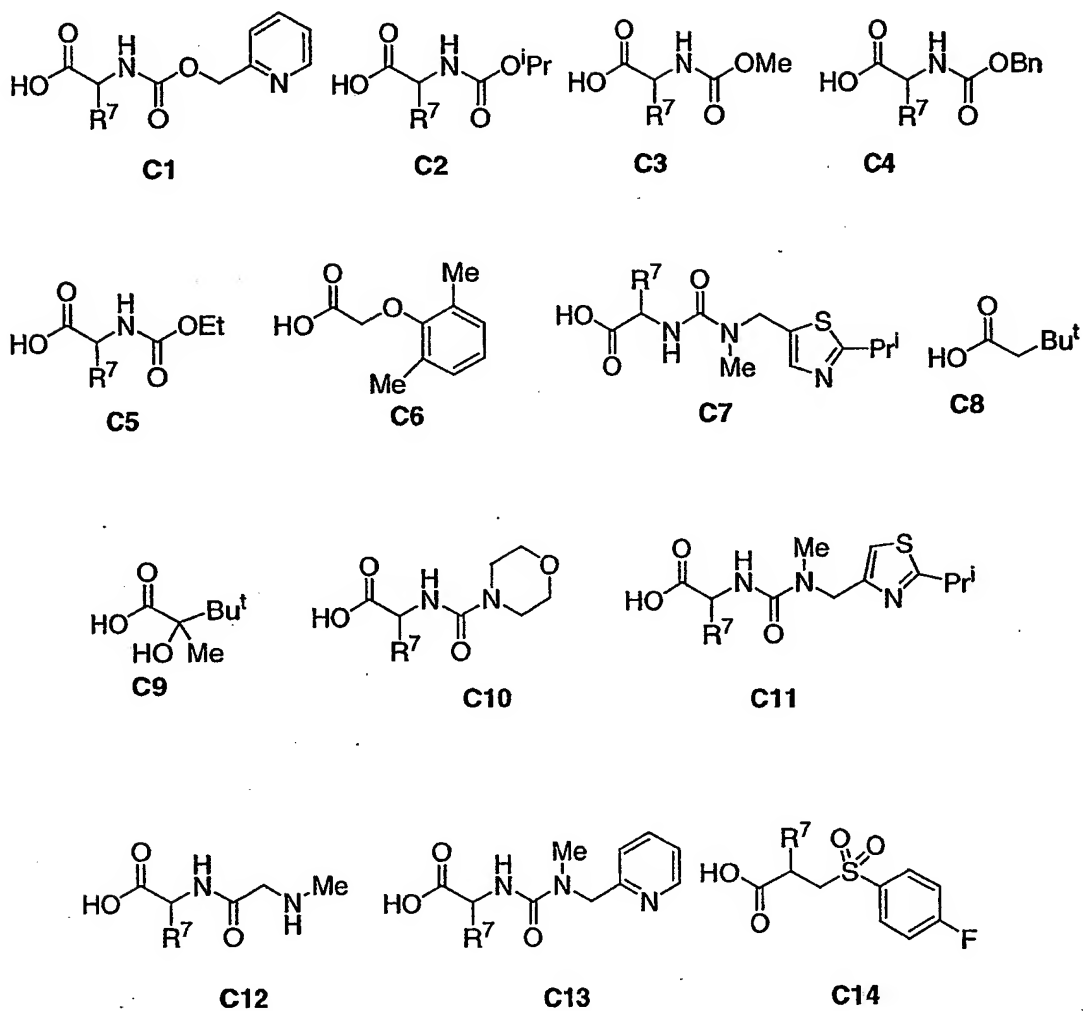
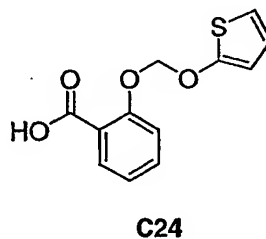
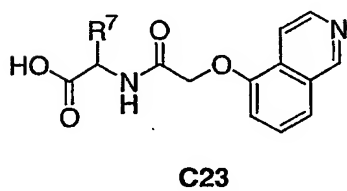
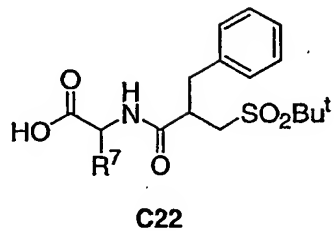
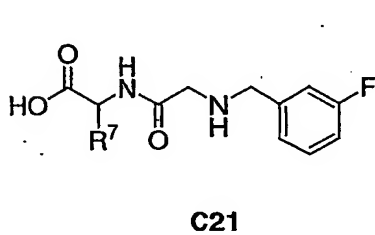
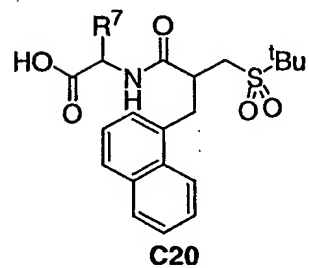
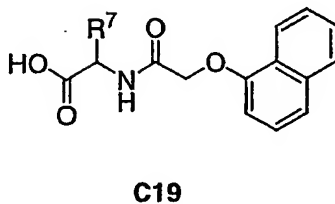
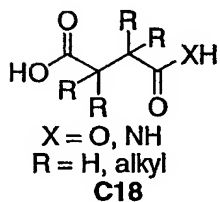
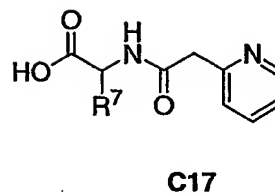
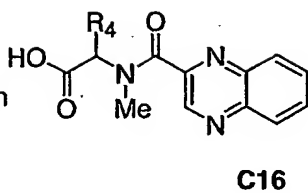
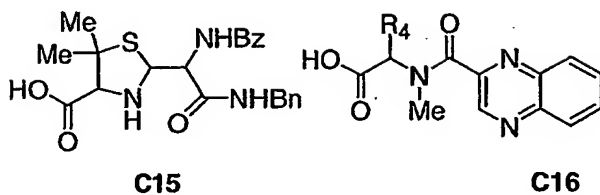
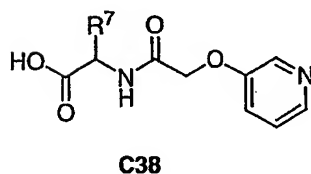
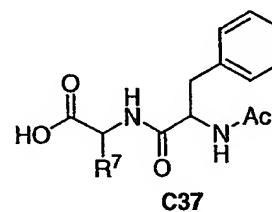
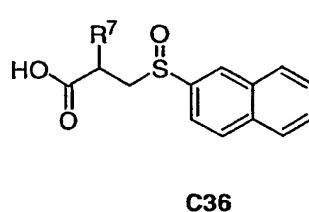
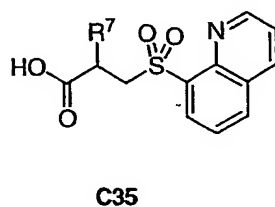
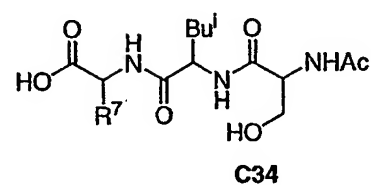
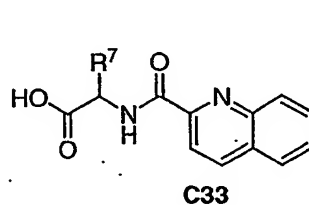
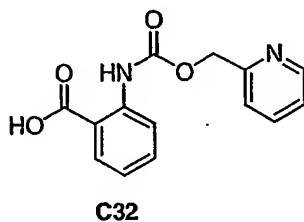
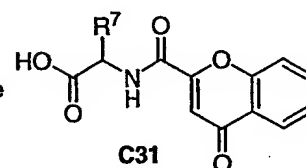
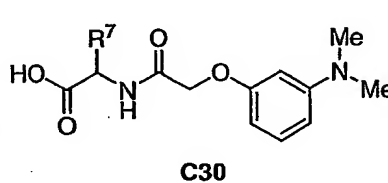
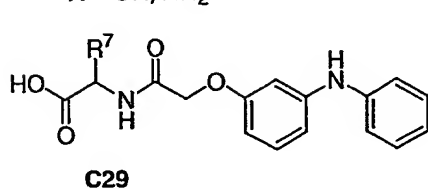
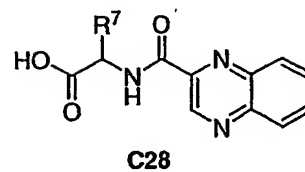
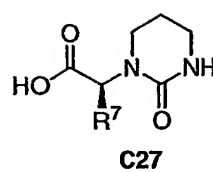
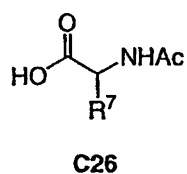
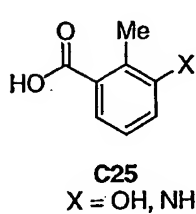


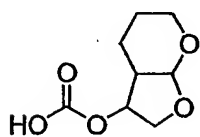
Chart 3a Structures of the R⁶COOH components



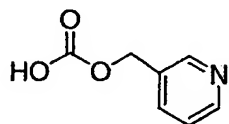
R^7 = alkyl, $\text{CH}_2\text{SO}_2\text{CH}_3$, $\text{C}(\text{CH}_3)_2\text{SO}_2\text{CH}_3$, CH_2CONH_2 , CH_2SCH_3 , imidaz-4-ylmethyl, CH_2NHAc , $\text{CH}_2\text{NHCOCF}_3$

Chart 3b Structures of the R⁶COOH components

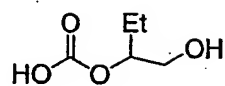
R⁷ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

Chart 3c Structures of the R⁶COOH components

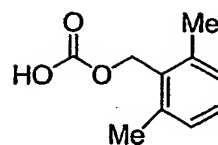
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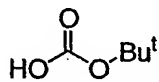
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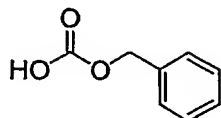
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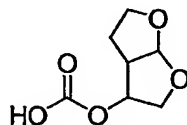
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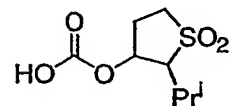
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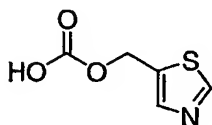
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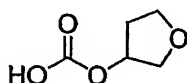
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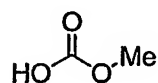
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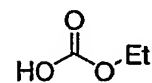
C46



C47



C48



C49

Chart 4 Examples of the linking group between the scaffold and the phosphonate moiety.

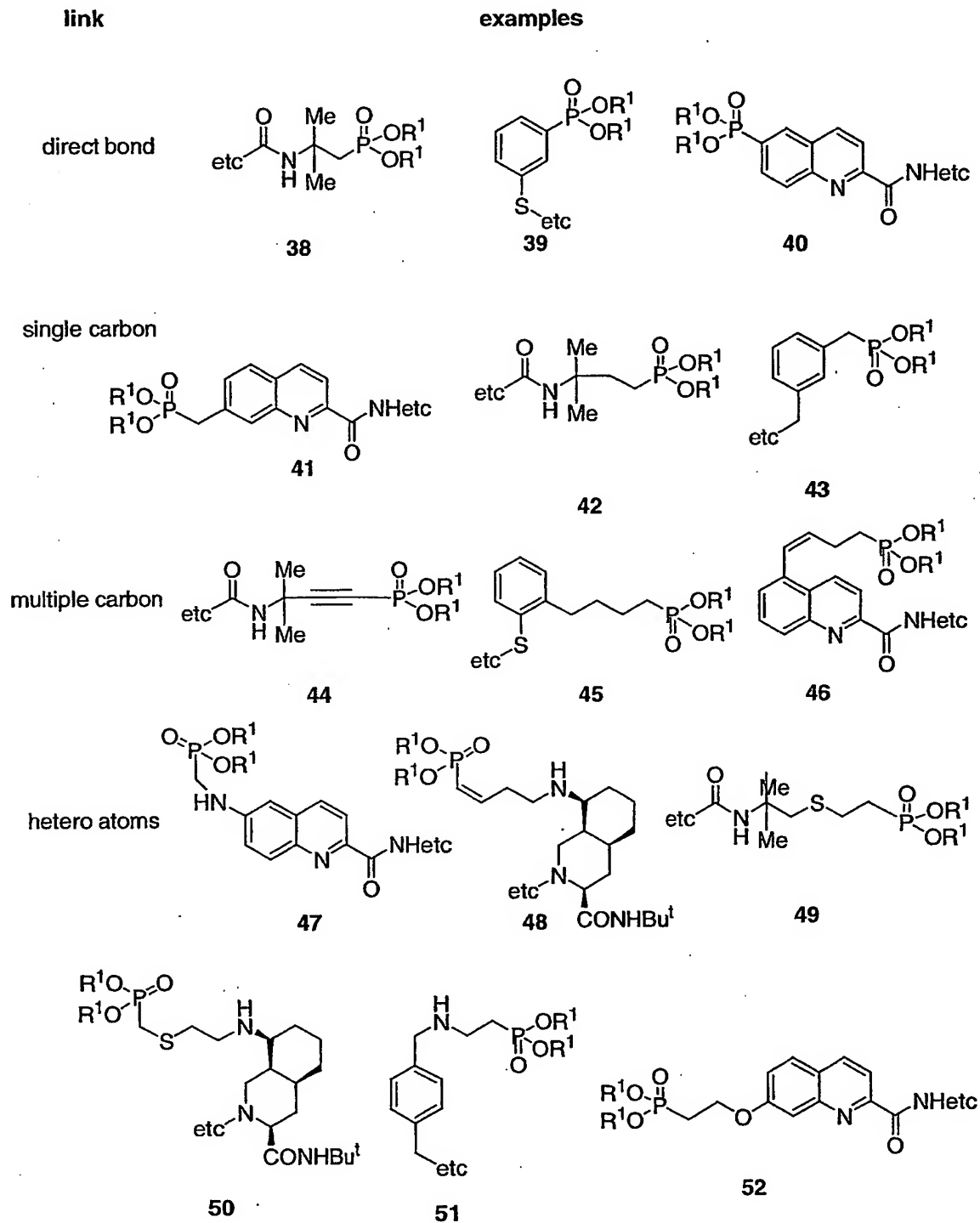
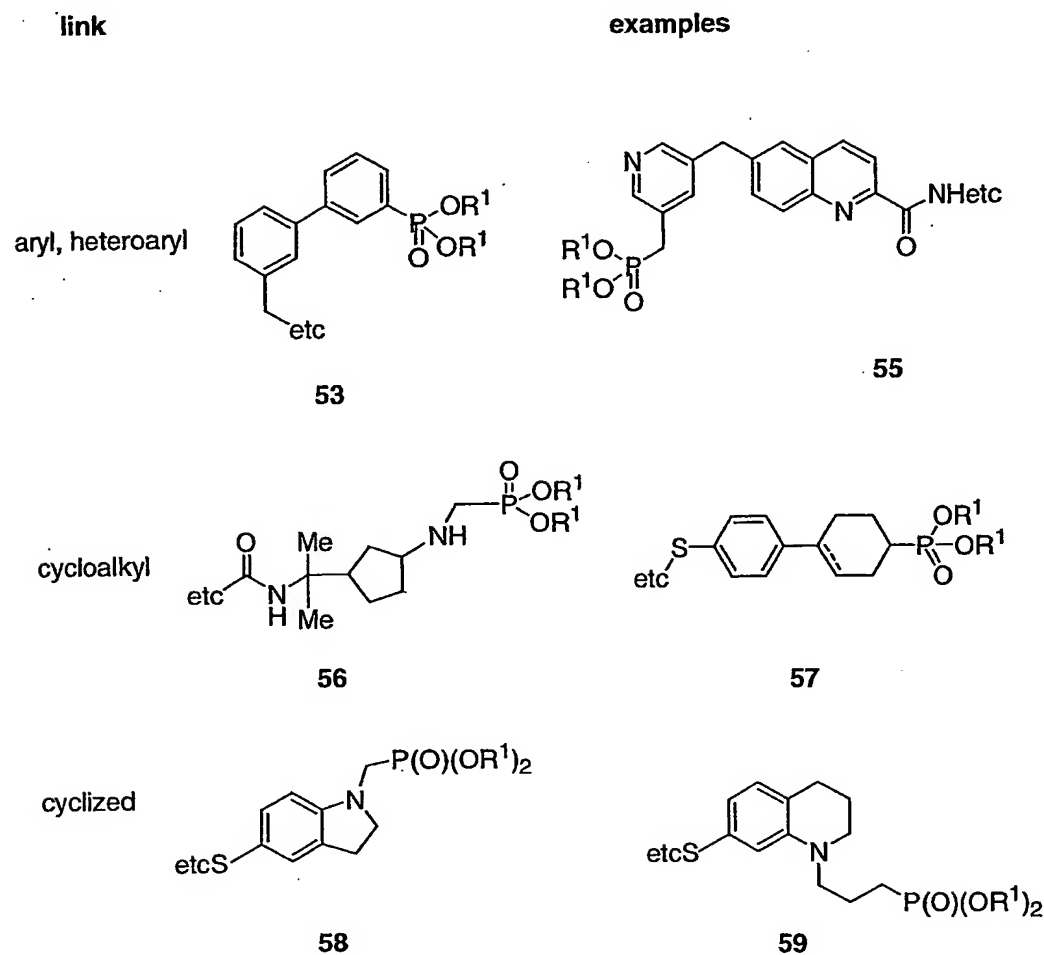


Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.

- Schemes 1 - 69 illustrate the syntheses of the intermediate phosphonate compounds of this invention, 1- 4, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters 5 and 6, in which the phosphonate moiety is incorporated into the groups $R^6\text{COOH}$ and $R^2\text{NHCH(R}^3\text{)CONHR}^4$, are also described below.

Protection of reactive substituents.

- Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the

art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

5

Preparation of the phosphonate intermediates 1.

Scheme 1 illustrates one method for the preparation of the phosphonate esters 1.6 in which X is a direct bond. In this procedure, an amine $R^2NHCH(R^3)CONHR^4$ 1.2 is reacted with an epoxide 1.1 to afford the aminoalcohol 1.3. The preparation of the epoxide 1.1 is described below, (Scheme 2) The preparation of aminoalcohols by reaction between an amine and an epoxide is described, for example, in Advanced Organic Chemistry, by J. March, McGraw Hill, 1968, p 334. In a typical procedure, equimolar amounts of the reactants are combined in a polar solvent such as an alcohol or dimethylformamide and the like, at from ambient to about 100°, for from 1 to 24 hours, to afford the product 1.3. The carbobenzyloxy protecting group is then removed. The removal of carbobenzyloxy protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 335. The reaction can be effected by means of catalytic hydrogenation in the presence of hydrogen or a hydrogen donor, by reaction with a Lewis acid such as aluminum chloride or boron tribromide, or by basic hydrolysis, for example employing barium hydroxide in an aqueous organic solvent mixture. Preferably, the protected amine 1.3 is converted into the free amine 1.4 by means of hydrogenation over 10% palladium on carbon catalyst in ethanol, as described in US Patent 5196438. The amine product 1.4 is then reacted with a carboxylic acid 1.5 to afford the amide 1.6. The coupling reaction of amines 1.4 and a carboxylic acid 1.5 can be effected under a variety of conditions, for example as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid can be activated by conversion to an imidazolid, mixed anhydride or active ester such as, for example, the ester with hydroxybenzotriazole or N-hydroxysuccinimide. Alternatively, the reactants can be combined in the presence of a carbodiimide, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, to afford the amide product 1.6. Preferably, equimolar amounts of the amine and the carboxylic acid are reacted in tetrahydrofuran at ca. -10°, in the presence of dicyclohexylcarbodiimide, as described in

U.S. Patent 5,196,438, to afford the amide 1.6. The carboxylic acid 1.5 employed in the above reaction is obtained by means of the reaction between the substituted quinoline-2-carboxylic acid 1.7, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor group thereto, such as [OH], [SH], Br, as described below, and an aminoacid 1.8.

- 5 The reaction is performed under similar conditions to those described above for the preparation of the amide 1.6. Preferably, the quinoline carboxylic acid 1.7 is reacted with N-hydroxy succinimide and a carbodiimide to afford the hydroxysuccinimide ester, which is then reacted with the aminoacid 1.8 in dimethylformamide at ambient temperature for 2-4 days, as described in U.S. Patent 5,196,438, to afford the amide product 1.5. The preparation of the
- 10 substituted quinoline carboxylic acids 1.7 is described below, Schemes 24-27.

- Scheme 2 illustrates the preparation of the epoxides 1.1 used above in Scheme 1. The preparation of the epoxide 1.1 in which R10 is H is described in J. Med. Chem., 1997, 40, 3979. Analogs in which R10 is one of the substituents defined in Chart 2 are prepared as
- 15 shown in Scheme 2. A substituted phenylalanine 2.1 is first converted into the benzyloxycarbonyl derivative 2.2. The preparation of benzyloxycarbonyl amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The aminoacid 2.1 is reacted with benzyl chloroformate or dibenzyl carbonate in the presence of a suitable base such as sodium carbonate or triethylamine, to
- 20 afford the protected amine product 2.2. The conversion of the carboxylic acid 2.2 into the epoxide 1.1 for example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, is then effected. The carboxylic acid is first converted into an activated derivative such as the acid chloride 2.3, in which X is Cl, for example by treatment with oxalyl chloride, or into a mixed carbonate, for example by treatment with isobutyl chloroformate, and
- 25 the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone 2.4. The reaction is performed by the addition of a solution of the activated carboxylic acid derivative to an ethereal solution of three or more molar equivalents of diazomethane at 0°C. The diazoketone is converted into the chloroketone 2.5 by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether, as described in J.
- 30 Med. Chem., 1997, 40, 3979. The latter compound is then reduced, for example by the use of an equimolar amount of sodium borohydride in an ethereal solvent such as tetrahydrofuran at 0°C, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer 2.6 is

separated by chromatography. The chlorohydrin 2.6 is then converted into the epoxide 1.1 by treatment with a base such as an alkali metal hydroxide in an alcoholic solvent, for example as described in J. Med. Chem., 1997, 40, 3979. Preferably, the compound 2.6 is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide 1.1.

5

Scheme 3 illustrates the preparation of the amine reactant $R^2NHCH(R^3)CONHR^4$ (1.2) employed above (Scheme 1). In this procedure, the carboxylic acid $R^2NHCH(R^3)COOH$ 3.1 is first converted into the N-protected analog 3.2, for example by reaction with benzyloxychloroformate and triethylamine in tetrahydrofuran. The carboxyl group is then

10 activated, for example by conversion to the acid chloride or a mixed anhydride, or by reaction with isobutyl chloroformate, as described in Chimia, 50, 532, 1996 and in Synthesis, 1972, 453, and the activated derivative is then reacted with the amine R^4NH_2 to produce the amide 3.4. Deprotection, for example as described above, then affords the free amine 1.2.

15 Scheme 4 depicts an alternative method for the preparation of the compounds 1 in which X is a direct bond. In this procedure, a hydroxymethyl-substituted oxazolidinone 4.1 is converted into an activated derivative 4.2 which is then reacted with the amine $R^2NHCH(R^3)CONHR^4$ (1.2) to afford the amide 4.3. The preparation of the hydroxymethyl-substituted oxazolidinone 4.1 is described below, (Scheme 5) The hydroxyl group can be converted into a bromo

20 derivative, for example by reaction with triphenylphosphine and carbon tetrabromide, as described in J. Am. Chem. Soc., 92, 2139, 1970, or a methanesulfonyloxy derivative, by reaction with methanesulfonyl chloride and a base, or, preferably, into the 4-nitrobenzenesulfonyloxy derivative 4.2, by reaction in a solvent such as ethyl acetate or tetrahydrofuran, with 4-nitrobenzenesulfonyl chloride and a base such as triethylamine or N-

25 methylmorpholine, as described in WO 9607642. The nosylate product 4.2 is then reacted with the amine component 1.2 to afford the displacement product 4.3. Equimolar amounts of the reactants are combined in an inert solvent such as dimethylformamide, acetonitrile or acetone, optionally in the presence of an organic or inorganic base such as triethylamine or sodium carbonate, at from about 0°C to 100°C to afford the amine product 4.3. Preferably, the

30 reaction is performed in methyl isobutyl ketone at 80°C, in the presence of sodium carbonate, as described in WO 9607642. The oxazolidinone group present in the product 4.3 is then hydrolyzed to afford the hydroxyamine 4.4. The hydrolysis reaction is effected in the presence

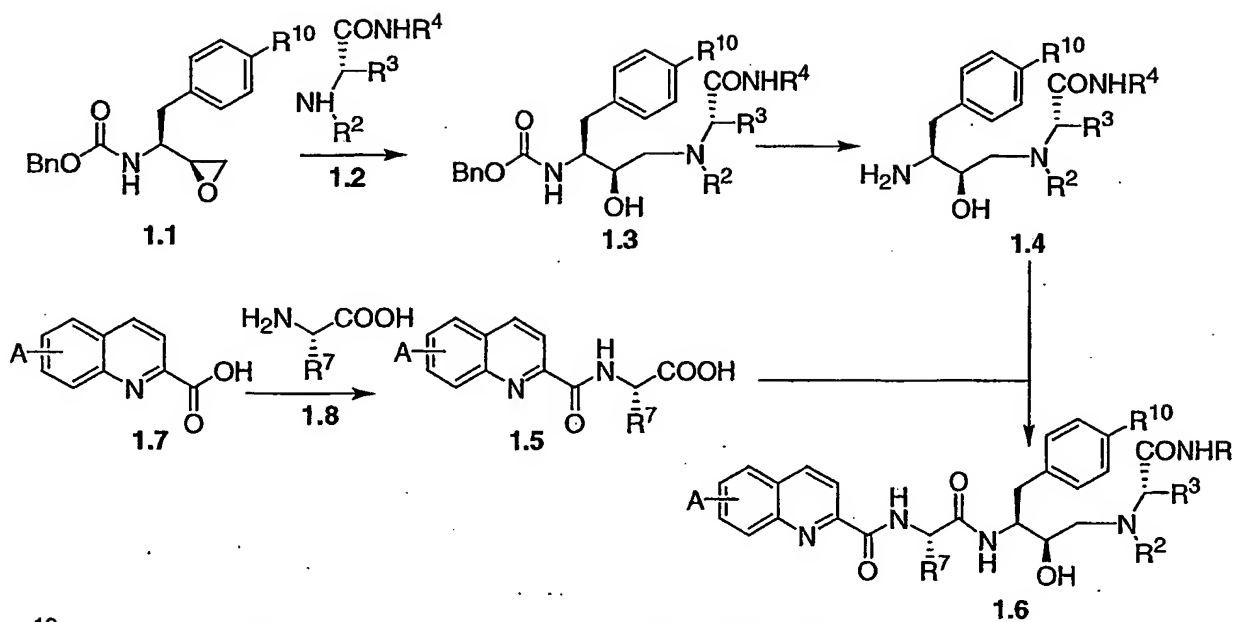
of aqueous solution of a base such as an alkali metal hydroxide, optionally in the presence of an organic co-solvent. Preferably, the oxazolidinone compound 4.3 is reacted with aqueous ethanolic sodium hydroxide at reflux temperature, as described in WO 9607642, to afford the amine 4.4. This product is then reacted with the carboxylic acid or activated derivative thereof, 1.5, the preparation of which is described above, to afford the product 1.6. The amide-forming reaction is conducted under the same conditions as described above, (Scheme 1)

Scheme 5 depicts the preparation of the hydroxymethyl oxazolidinones 4.1, which are utilized in the preparation of the phosphonate esters 1, as described above in Scheme 4. In this procedure, phenylalanine, or a substituted derivative thereof, 2.1, in which R¹⁰ is as defined in Chart 2, is converted into the phthalimido derivative 5.1. The conversion of amines into phthalimido derivatives is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 358. The amine is reacted with phthalic anhydride, 2-carboethoxybenzoyl chloride or N-carboethoxyphthalimide, optionally in the presence of a base such as triethylamine or sodium carbonate, to afford the protected amine 5.1. Preferably, the amino acid is reacted with phthalic anhydride in toluene at reflux, to yield the phthalimido product. The carboxylic acid is then transformed into an activated derivative such as the acid chloride 5.2, in which X is Cl. The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of a tertiary amide such as dimethylformamide. Preferably, the carboxylic acid is transformed into the acid chloride by reaction with oxalyl chloride and a catalytic amount of dimethylformamide, in toluene solution at ambient temperature, as described in WO 9607642. The acid chloride 5.2, X = Cl, is then converted into the aldehyde 5.3 by means of a reduction reaction. This procedure is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 620. The transformation can be effected by means of catalytic hydrogenation, a procedure which is referred to as the Rosenmund reaction, or by chemical reduction employing, for example, sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride or triethylsilane. Preferably, the acid chloride 5.2 X = Cl, is hydrogenated in toluene solution over a 5% palladium on carbon catalyst, in the presence of

butylene oxide, as described in WO 9607642, to afford the aldehyde 5.3. The aldehyde 5.3 is then transformed into the cyanohydrin derivative 5.4. The conversion of aldehydes into cyanohydrins is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 211. For example, the aldehyde 5.3 is converted
5 into the cyanohydrin 5.4 by reaction with trimethylsilyl cyanide in an inert solvent such as dichloromethane, followed by treatment with an organic acid such as citric acid, as described in WO 9607642, or by alternative methods described therein. The cyanohydrin is then subjected to acidic hydrolysis, to effect conversion of the cyano group into the corresponding carboxy group, with concomitant hydrolysis of the phthalimido substituent to afford the
10 aminoacid 5.5. The hydrolysis reactions are effected by the use of aqueous mineral acid. For example, the substrate 5.4 is reacted with aqueous hydrochloric acid at reflux, as described in WO 9607642, to afford the carboxylic acid product 5.5. The aminoacid is then converted into a carbamate, for example the ethyl carbamate 5.6. The conversion of amines into carbamates is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts,
15 Wiley, Second Edition 1990, p. 317. The amine is reacted with a chloroformate, for example ethyl chloroformate, in the presence of a base such as potassium carbonate, to afford the carbamate 5.6. For example, the aminoacid 5.5 is reacted, in aqueous solution, with ethyl chloroformate and sufficient aqueous sodium hydroxide to maintain a neutral pH, as described in WO 9607642, to afford the carbamate 5.6. The latter compound is then transformed into
20 the oxazolidinone 5.7, for example by treatment with aqueous sodium hydroxide at ambient temperature, as described in WO 9607642. The resultant carboxylic acid is transformed into the methyl ester 5.8 by means of a conventional esterification reaction. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by
25 means of an acid-catalyzed reaction between the carboxylic acid and an alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and an alkyl halide, for example an alkyl bromide. For example, the carboxylic acid 5.7 is converted into the methyl ester 5.8 by treatment with methanol at reflux temperature, in the presence of a catalytic amount of sulfuric acid, as described in WO 9607642. The carbomethoxyl group present in the compound 5.8 is
30 then reduced to yield the corresponding carbinol 4.1. The reduction of carboxylic esters to the carbinols is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 550. The transformation can be effected by the use of reducing agents such as

borane-dimethylsulfide, lithium borohydride, diisobutyl aluminum hydride, lithium aluminum hydride and the like. For example, the ester **5.8** is reduced to the carbinol **4.1** by reaction with sodium borohydride in ethanol at ambient temperature, as described in WO 9607642.

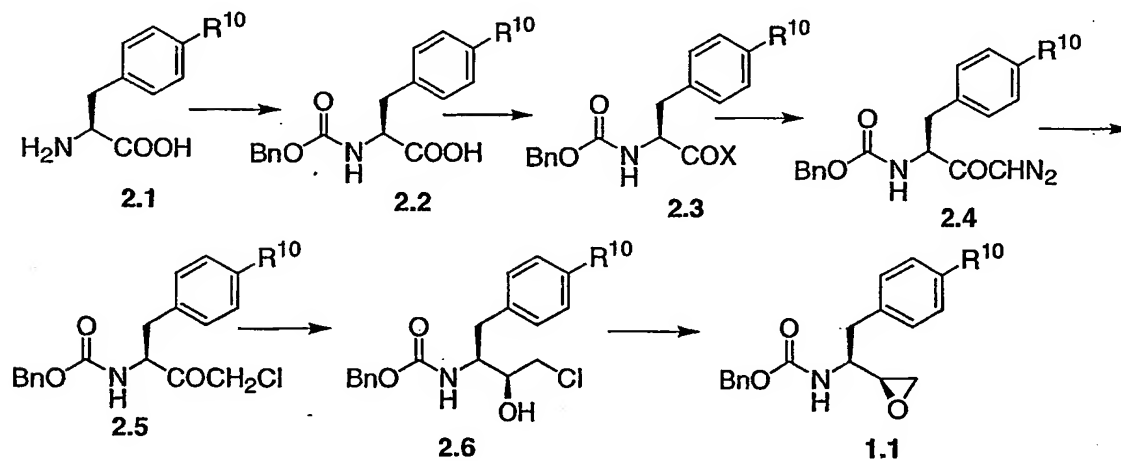
Scheme 1



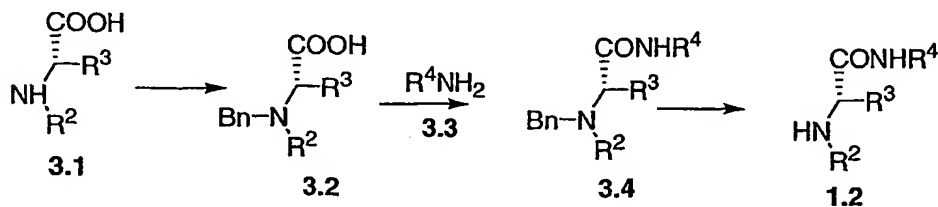
$R^{10} = H, OC_2H_5, OCH_2C_6H_5, OCH_2CH_2\text{morpholino}, OCH_2COMorpholino$

$A = [OH], [SH], [NH_2], Br$ etc or link- $P(O)(OR^1)_2$

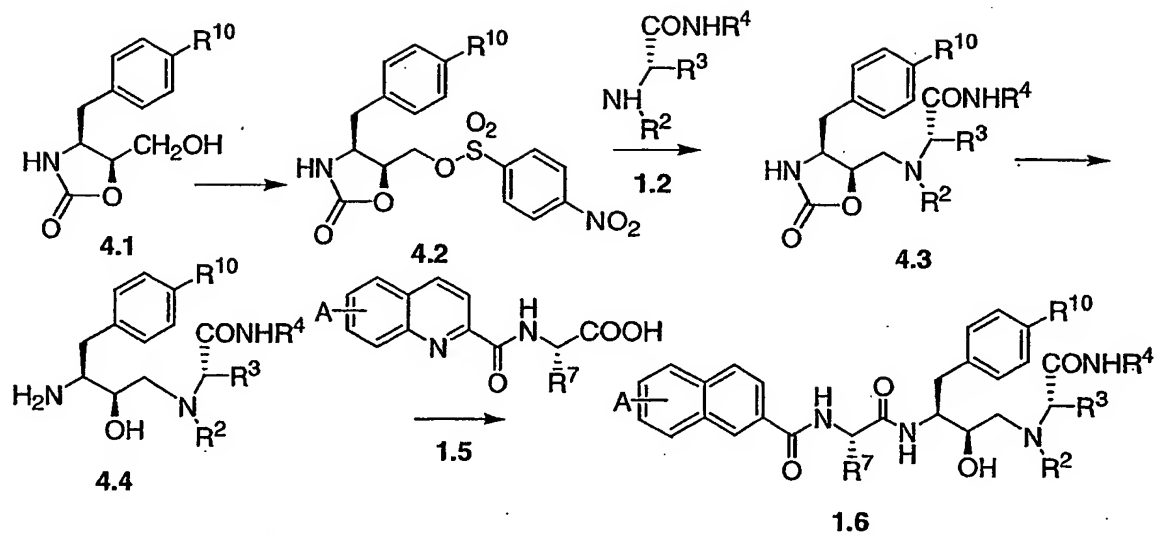
Scheme 2



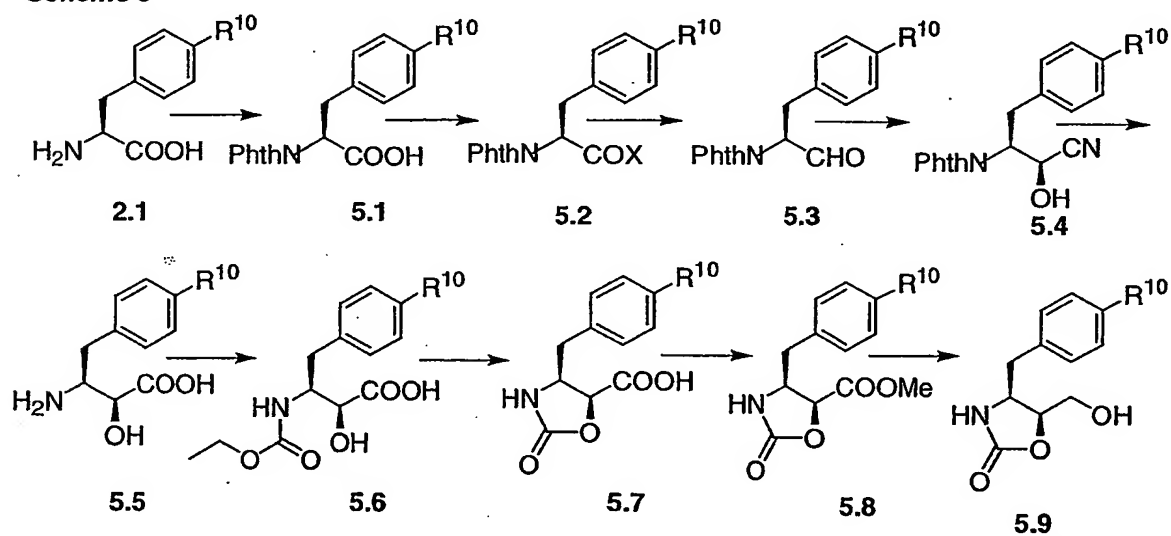
Scheme 3



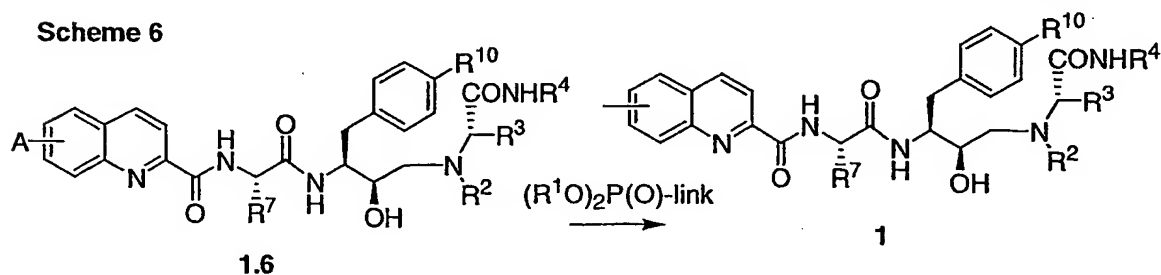
Scheme 4



Scheme 5



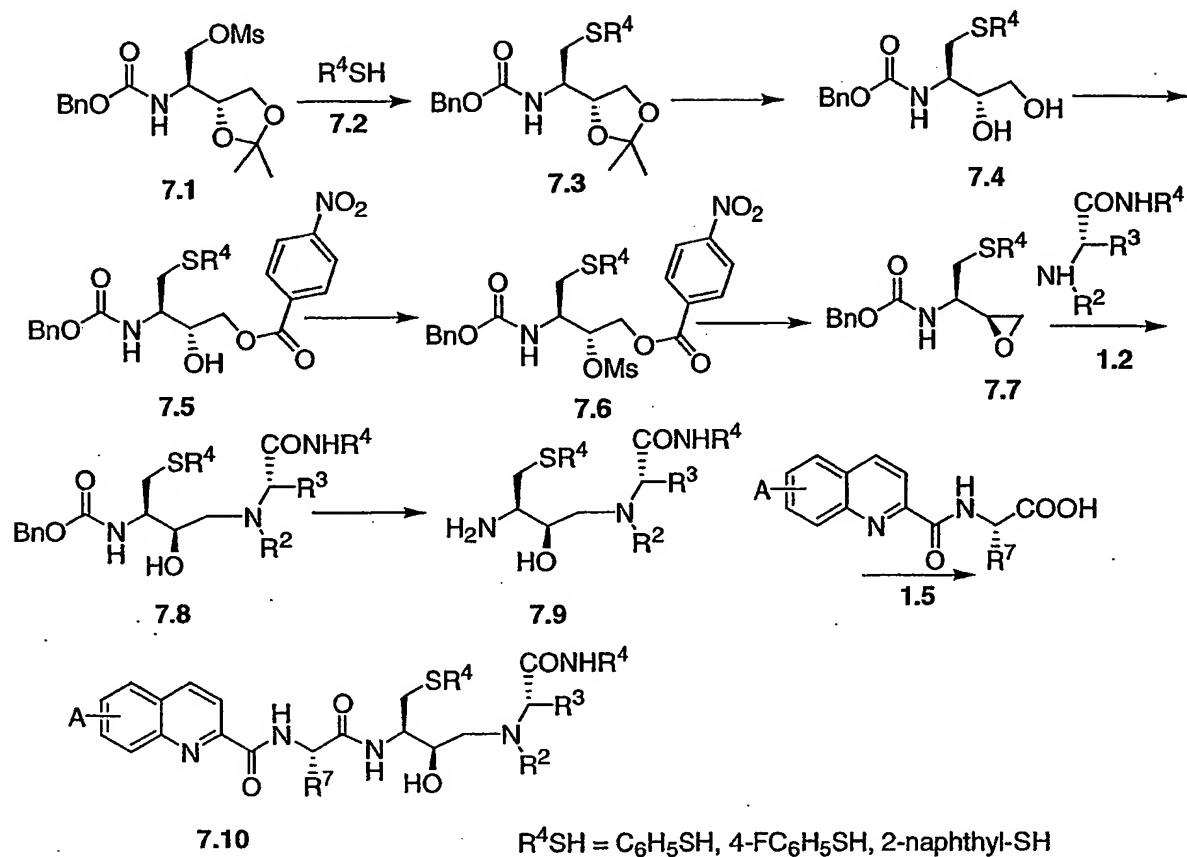
Scheme 6



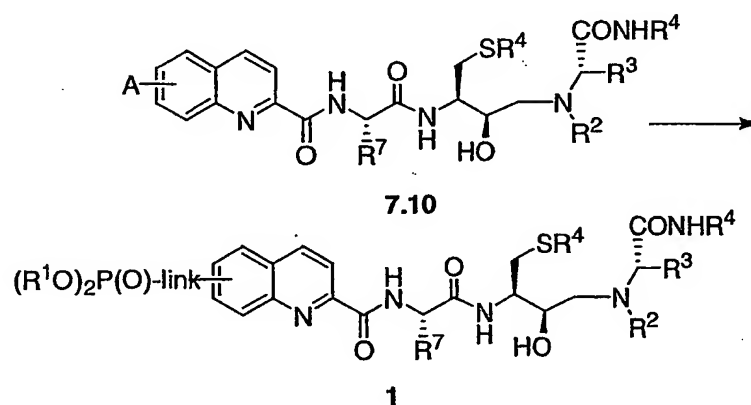
The procedures illustrated in Schemes 1 and 4 depict the preparation of the compounds 1.6 in which X is a direct bond, and in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 6 illustrates the conversion of compounds 1.6 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 1. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 24 - 69). In the procedures illustrated above, Schemes 1, 4 and in the procedures illustrated below (Schemes 24-69) for the preparation of the phosphonate esters 2-6, compounds in which the group A is a precursor to the group link-P(O)(OR¹)₂ may be converted into compounds in which A is link-P(O)(OR¹)₂ at any appropriate stage in the reaction sequence, or, as shown in Scheme 6, at the end of the sequence. The selection of an appropriate stage to effect the conversion of the group A into the group link-P(O)(OR¹)₂ is made after consideration of the nature of the reactions involved in the conversion, and the stability of the various components of the substrate to those conditions.

15

Scheme 7



Scheme 8



Scheme 7 illustrates the preparation of the compounds 1 in which the substituent X is S, and in which the group A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH],

5 [SH] Br, as described below.

In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, **7.1**, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol R^4SH **7.2**, as defined above, to afford the thioether **7.3**.

The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the like, in the presence of an inorganic or organic base, at from 0°C to 80°C, for from 1-12 hours, to afford the thioether **7.3**. Preferably the mesylate **7.1** is reacted with an equimolar amount of the thiol R^4SH , in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°C, to give the product **7.3**. The 1,3-dioxolane protecting group present in the compound **7.3** is then removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol **7.4**. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p. 191. For example, the 1,3-dioxolane compound **7.3** is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane **7.3** is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°C, to yield the product **7.4**.

The primary hydroxyl group of the diol **7.4** is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as dichloromethane and the like, in the presence of an inorganic or organic base.

Preferably, equimolar amounts of the diol **7.4** and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the hydroxy ester **7.5**. The hydroxy ester is next reacted with a sulfonyl chloride such as methanesulfonyl chloride, 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the corresponding sulfonyl ester **7.6**. Preferably, equimolar amounts of the carbinol **7.5** and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the mesylate **7.6**. The compound **7.6** is then subjected to a hydrolysis-cyclization reaction to afford the oxirane **7.7**. The mesylate or analogous leaving group present in **7.6** is displaced by hydroxide ion, and the carbinol thus produced, without isolation, spontaneously transforms into the oxirane **7.7** with elimination of 4-nitrobenzoate. To effect

this transformation, the sulfonyl ester 7.6 is reacted with an alkali metal hydroxide or tetraalkylammonium hydroxide in an aqueous organic solvent. Preferably, the mesylate 7.6 is reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour, to afford the oxirane 7.7.

- 5 The oxirane compound 7.7 is then subjected to regiospecific ring-opening reaction by treatment with a secondary amine 1.2, to give the aminoalcohol 7.8. The amine and the oxirane are reacted in a protic organic solvent, optionally in the additional presence of water, at 0°C to 100°C, and in the presence of an inorganic base, for 1 to 12 hours, to give the product 7.8. Preferably, equimolar amounts of the reactants 7.7 and 1.2 are reacted in
- 10 aqueous methanol at about 60°C in the presence of potassium carbonate, for about 6 hours, to afford the aminoalcohol 7.8. The carbobenzyloxy (cbz) protecting group in the product 7.8 is removed to afford the free amine 7.9. Methods for removal of cbz groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition, p. 335. The methods include catalytic hydrogenation and acidic or basic
- 15 hydrolysis.

- For example, the cbz-protected amine 7.8 is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or alcoholic solvent, to yield the free amine 7.9. Preferably, the cbz group is removed by the reaction of 7.8 with potassium hydroxide in an alcohol such as isopropanol at ca. 60°C to afford the amine 7.9. The amine 7.9 so obtained is next acylated
- 20 with a carboxylic acid or activated derivative 1.5, using the conditions described above for the conversion of the amine 1.4 into the amide 1.6 (Scheme 1), to yield the final amide product 7.10.

- The procedures illustrated in Scheme 7 depict the preparation of the compounds 1 in which X is S, and in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 8 illustrates the conversion of
- 25 compounds 7.10 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 1. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 24 - 69).

- 30 The reactions illustrated in Schemes 1-7 illustrate the preparation of the compounds 1 in which A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as, for example, optionally protected OH, SH, NH, as described below. Scheme 8 depicts the conversion of the

compounds 1 in which A is OH, SH, NH, as described below, into the compounds 1 in which A is the group link-P(O)(OR¹)₂. Procedures for the conversion of the group A into the group link-P(O)(OR¹)₂ are described below, (Schemes 24-69).

In this and succeeding examples, the nature of the phosphonate ester group can be varied,
5 either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below, (Scheme 54)

Preparation of the phosphonate intermediates 2.

10

Scheme 9 depicts the one method for the preparation of the compounds 2 in which X is a direct bond, and in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. In this procedure, the hydroxymethyl oxazolidinone 9.1, the preparation of which is described below, is converted into an activated
15 derivative, for example the 4-nitrobenzenesulfonate 9.2. The conditions for this transformation are the same as those described above (Scheme 4) for the conversion of the carbinol 4.1 into the nosylate 4.2. The activated ester 9.2 is then reacted with the amine 1.2, under the same conditions as described above for the preparation of the amine 4.3 to afford the oxazolidinone amine 9.3. The oxazolidinone group is then hydrolyzed by treatment with
20 aqueous alcoholic base, to produce the primary amine 4.4. For example, the oxazolidinone 9.3 is reacted with aqueous ethanolic sodium hydroxide at reflux temperature, as described in WO 9607642, to afford the amine product 9.4. The latter compound is then coupled with the carboxylic acid 9.6, to afford the amide 9.5. The conditions for the coupling reaction are the same as those described above for the preparation of the amide 1.6.

25 The phosphonate esters 2 - 6 which incorporate the group R⁶ CO derived formally from the carboxylic acids depicted in Chart 2c contain a carbamate group. Various methods for the preparation of carbamates are described below, (Scheme 55)

Scheme 10 illustrates an alternative method for the preparation of the compounds 2 in which
30 X is a direct bond, and in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. In this procedure, the oxirane 10.1, the preparation of which is described below, is reacted with the amine 1.2 to afford the

aminoalcohol 10.2. The reaction is conducted under the same conditions as are described above for the preparation of the aminoalcohol 1.3. (Scheme 1) The benzyloxycarbonyl protecting group is then removed from the product 10.2 to afford the free amine 10.3. The conditions for the debenzoylation reaction are the same as those described above for the debenzoylation of the compound 1.3. The amine 10.3 is then coupled with the carboxylic acid 9.6 to produce the amide 9.5, employing the same conditions as are described above (Scheme 9).

The procedures illustrated in Schemes 9 and 10 depict the preparation of the compounds 9.5 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 11 illustrates the conversion of compounds 9.5 in which A is a precursor to the group $\text{link-P(O)(OR}^1)_2$ into the compounds 2. Procedures for the conversion of the substituent A into the group $\text{link-P(O)(OR}^1)_2$ are illustrated below, (Schemes 24 -69).

15

Schemes 12 and 13 depict the preparation of compounds 2 in which X is sulfur. As shown in Scheme 12, a substituted thiophenol 12.2, in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, is reacted with methanesulfonic acid 2-benzyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester 12.1, the preparation of which is described in J. Org. Chem, 2000, 65, 1623, to afford the displacement product 12.3. The conditions for the reaction are the same as described above for the preparation of the thioether 7.3. Methods for the preparation of the substituted thiophenol 12.2 are described below, Schemes 35 - 44. The thioether product 12.3 is then transformed, using the series of reactions described above, Scheme 7, for the conversion of the thioether 7.3 into the amine 7.9. The conditions employed for this series of reactions are the same as those described above, (Scheme 7). The amine 12.4 is then reacted with the carboxylic acid or activated derivative thereof, 9.6 to afford the amide 12.5. The conditions for the reaction are the same as those described above for the preparation of the amide 9.5.

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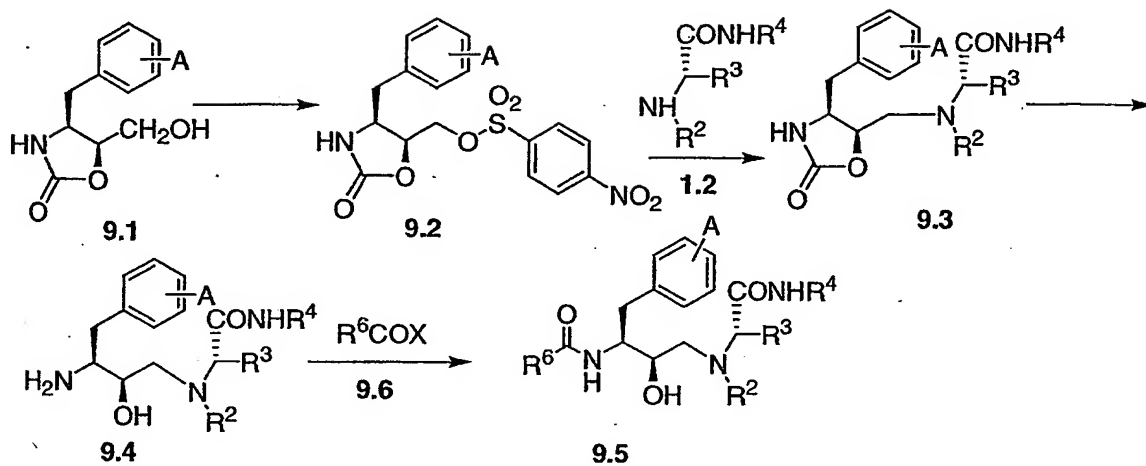
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The procedures illustrated in Scheme 12 depict the preparation of the compounds 12.5 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 13 illustrates the conversion of compounds 12.5

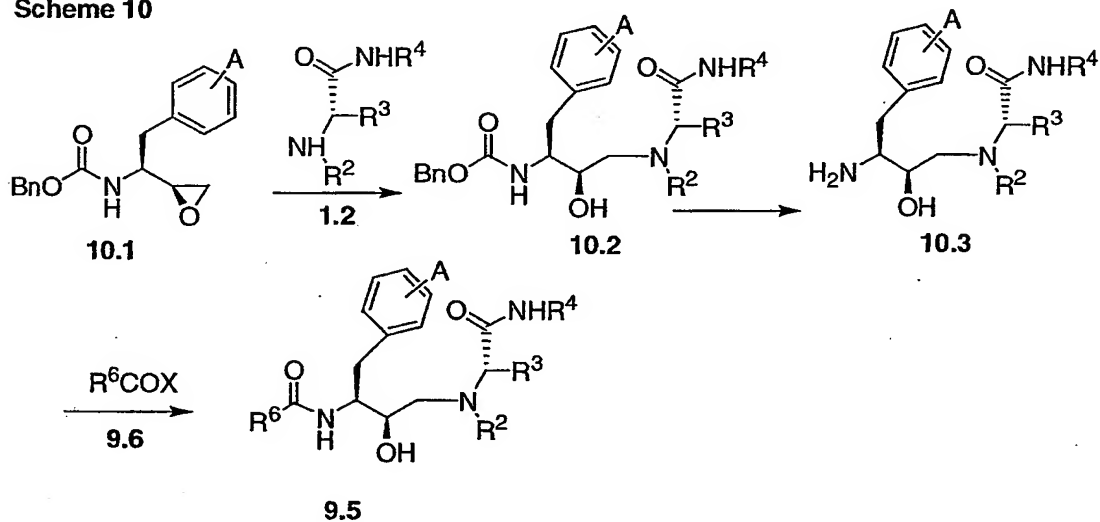
30

in which A is a precursor to the group $\text{link-P(O)(OR}^1\text{)}_2$ into the compounds 2. Procedures for the conversion of the substituent A into the group $\text{link-P(O)(OR}^1\text{)}_2$ are illustrated below, (Schemes 24 - 69).

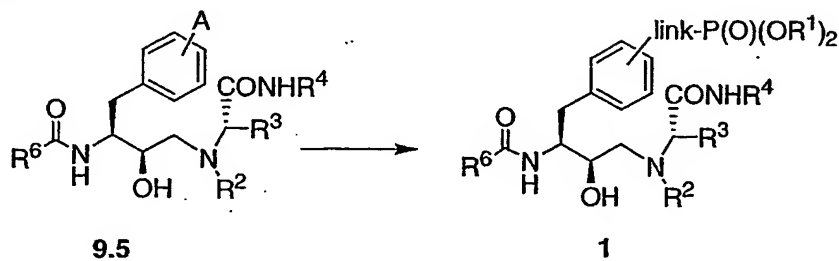
Scheme 9



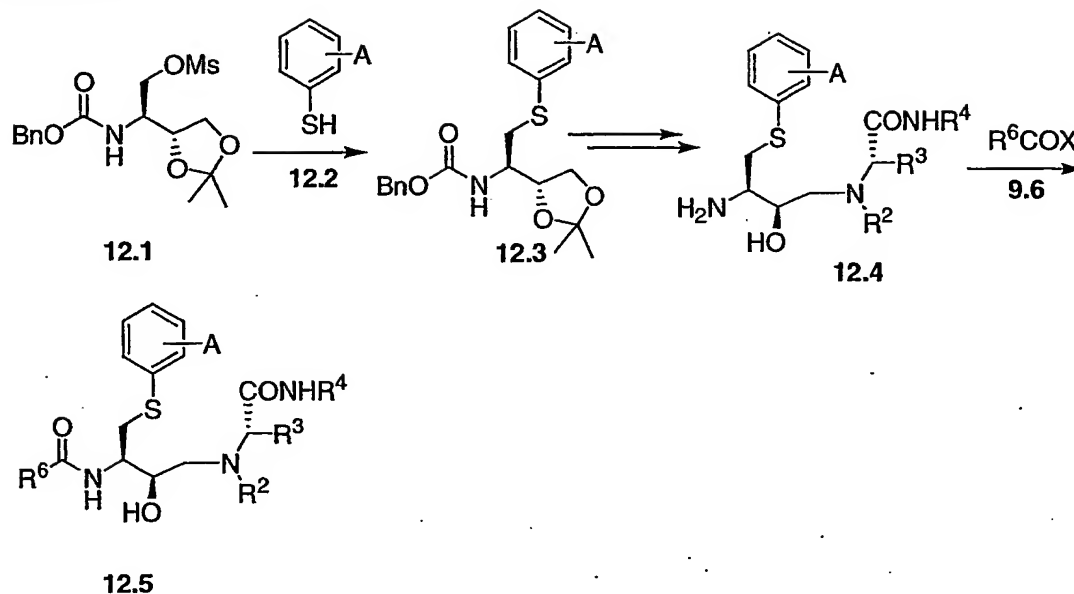
Scheme 10



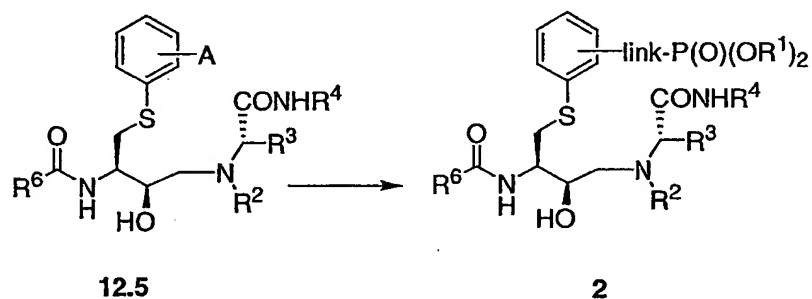
Scheme 11



Scheme 12



Scheme 13



5

Preparation of the phosphonate intermediates 3.

Schemes 14-16 depict the preparation of the phosphonate esters 3 in which X is a direct bond. As shown in Scheme 14, the oxirane 1.1, the preparation of which is described above, is reacted with the amine 14.1 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as $[\text{OH}]$, $[\text{SH}]$ Br, as described below, to yield the hydroxyamine 14.2. The conditions for the reaction are the same as described above for the preparation of the amine 1.3. Methods for the preparation of the amine 14.1 are described below, Schemes 45 -

48. The hydroxyamine product 14.2 is then deprotected to afford the free amine 14.3. The conditions for the debenzylation reaction are the same as those described above for the preparation of the amine 1.4. (Scheme 1). The amine 14.3 is then coupled with the carboxylic acid or activated derivative thereof, 9.6, to afford the amide 14.4, using the conditions described above for the preparation of the amide 12.5.

Scheme 15 illustrates an alternative method for the preparation of the phosphonate esters 14.4. In this reaction sequence, the 4-nitrobenzenesulfonate 4.2, the preparation of which is described above, (Scheme 4), is reacted with the amine 14.1, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below, to yield the amine 15.1. The reaction is conducted under the same conditions as described above for the preparation of the amide 4.3. The oxazolidine moiety present in the product is then removed, using the procedure described above for the conversion of the oxazolidine 4.3 into the hydroxyamine 4.4, to afford the hydroxyamine 15.2. The latter compound is then coupled, as described above, with the carboxylic acid or activated derivative thereof, 9.6, to afford the amide 14.4.

The procedures illustrated in Schemes 14 and 15 depict the preparation of the compounds 14.4 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 16 illustrates the conversion of compounds 14.4 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 3. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 24 - 69).

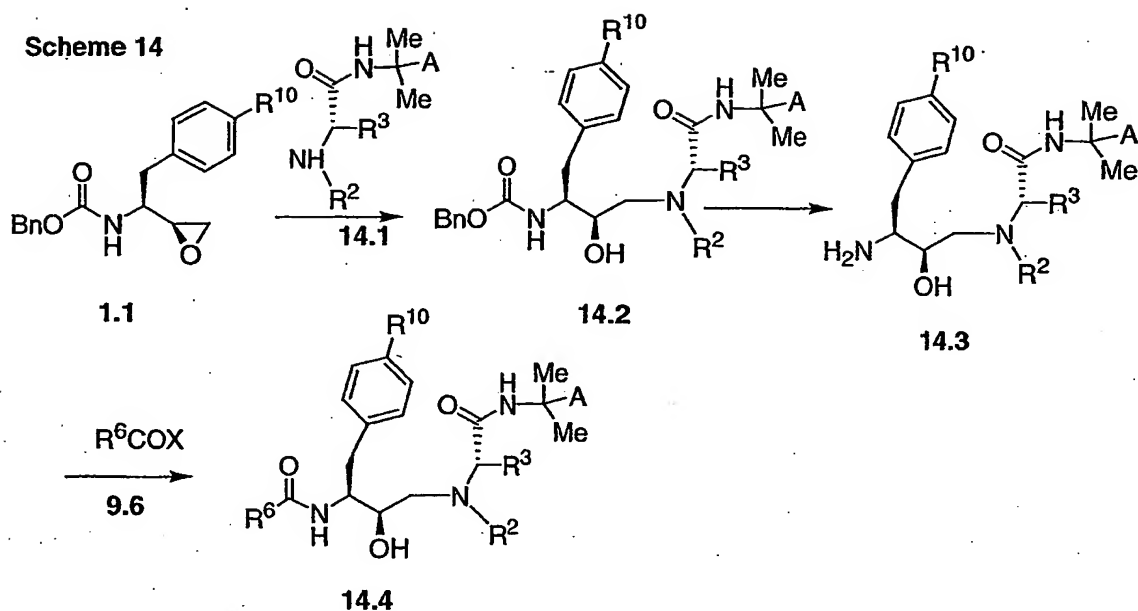
Schemes 17 and 18 illustrates the preparation of the phosphonate esters 3 in which X is sulfur. As shown in Scheme 17, the oxirane 7.7, the preparation of which is described above, (Scheme 7) is reacted with the amine 14.1. The conditions for the ring-opening reaction are the same as those described above for the preparation of the aminoalcohol 7.8, (Scheme 7). The benzyloxycarbonyl protecting group is then removed to produce the free amine 17.2. The conditions for the deprotection reaction are the same as those described above for the conversion of the protected amine 7.8 to the amine 7.9 (Scheme 7) The amine product 17.2 is

then coupled with the carboxylic acid or activated derivative thereof, **9.6**, using the same conditions as described above, to afford the amide **17.3**.

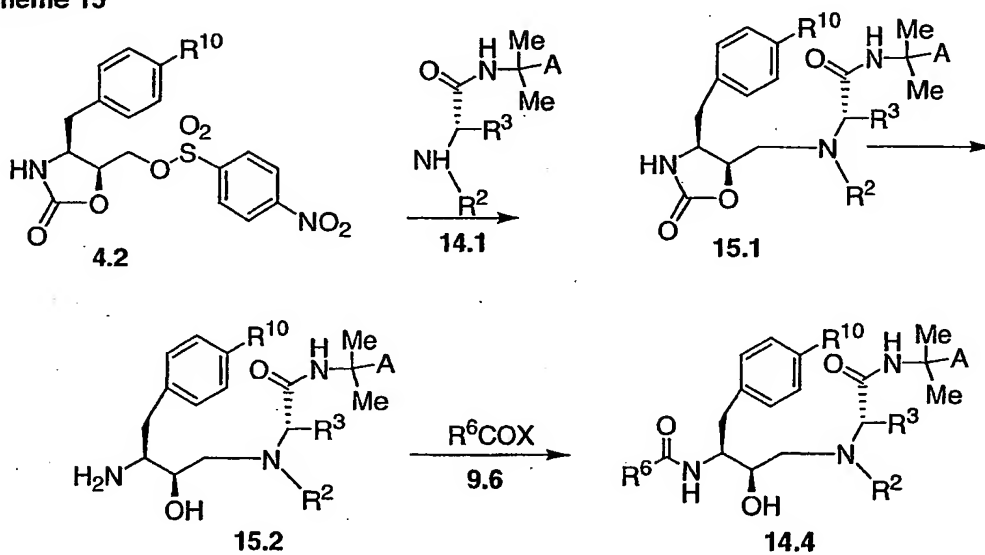
5 The procedures illustrated in Scheme 17 depict the preparation of the compound **17.3** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 18 illustrates the conversion of compounds **17.3** in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds **3**. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 24 - 69).

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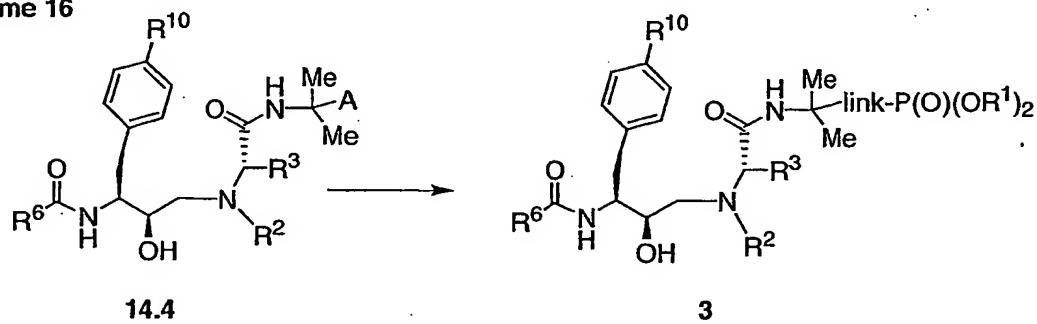
Scheme 14



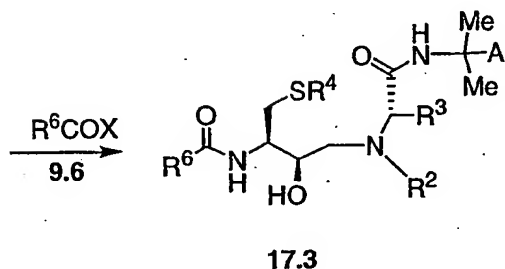
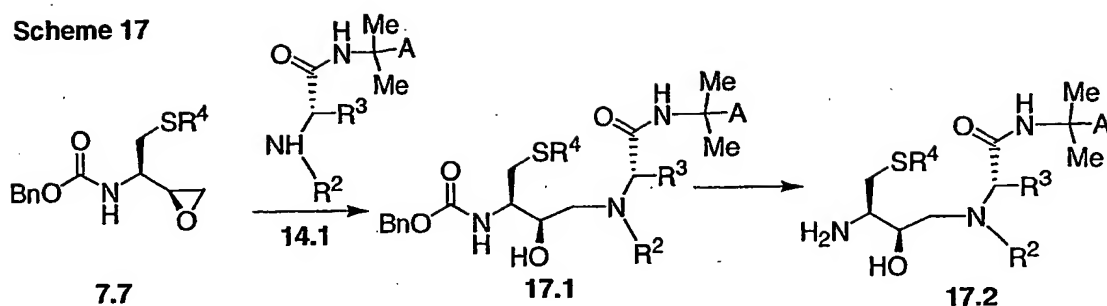
Scheme 15



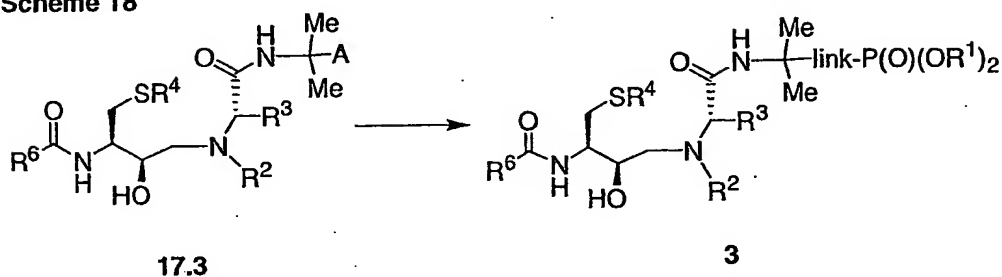
Scheme 16



Scheme 17



Scheme 18



5 Preparation of the phosphonate intermediates 4.

Scheme 19 illustrates one method for the preparation of the phosphonate esters 4 in which X is a direct bond. In this reaction sequence, the oxirane 1.1, the preparation of which is described above (Scheme 2) is reacted with the decahydroisoquinoline amine 19.1, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below, to afford the aminoalcohol product 19.2. The conditions for the ring-opening reaction are the same as those described above for the preparation of the aminoalcohol 1.3. The preparation of the decahydroisoquinoline derivatives 19.1 is described below, (Schemes 48a - 52). The cbz protecting group is then removed to yield the free amine 19.3, using the same conditions as described above for the preparation of the amine 1.4,

(Scheme 1). The amine 19.3 is then coupled with the carboxylic acid or activated derivative thereof, 9.6, using the same conditions as described above, to afford the amide 19.4.

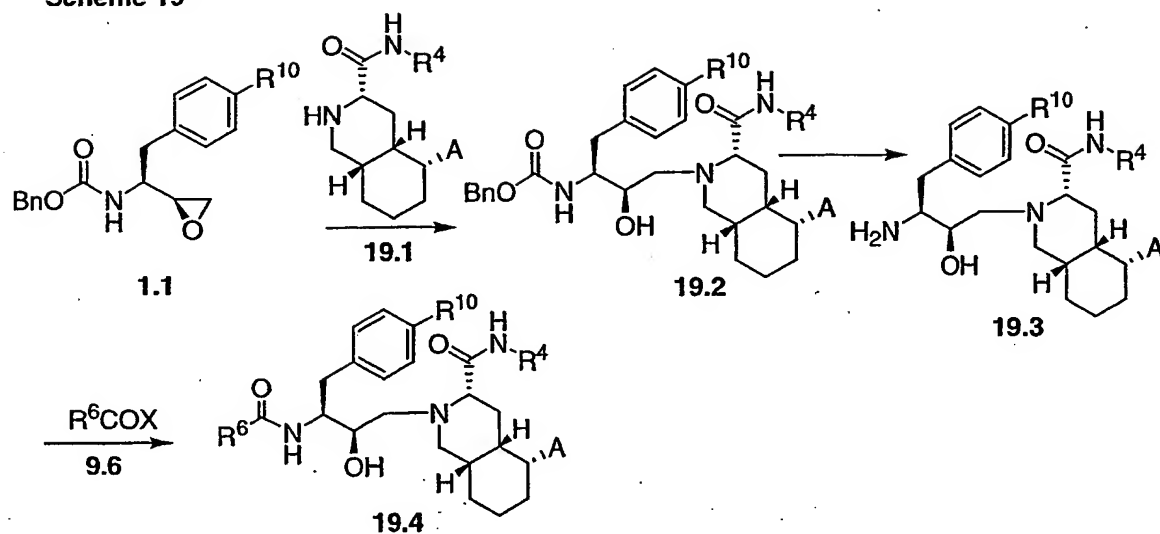
Scheme 20 illustrates an alternative method for the preparation of the phosphonate intermediates 19.4. In this procedure, the 4-nitrobenzenesulfonyl ester 4.2, the preparation of which is described above, (Scheme 4) is reacted with the decahydroisoquinoline derivative 20.1, in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. The reaction conditions for the displacement reaction are the same as those described above for the preparation of the amine 4.3, (Scheme 4). The oxazolidinone moiety present in the product 20.2 is then hydrolyzed, using the procedures described above (Scheme 4) to afford the free amine 20.3. This compound is then coupled with the carboxylic acid or activated derivative thereof, 9.6, using the same conditions as are described above, to afford the amide product 19.4.

The procedures illustrated in Schemes 19 and 20 depict the preparation of the compounds 19.4 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 21 illustrates the conversion of compounds 19.4 in which A is a precursor to the group $\text{link-P(O)(OR}^1\text{)}_2$ into the compounds 4. Procedures for the conversion of the substituent A into the group $\text{link-P(O)(OR}^1\text{)}_2$ are illustrated below, (Schemes 24 - 69).

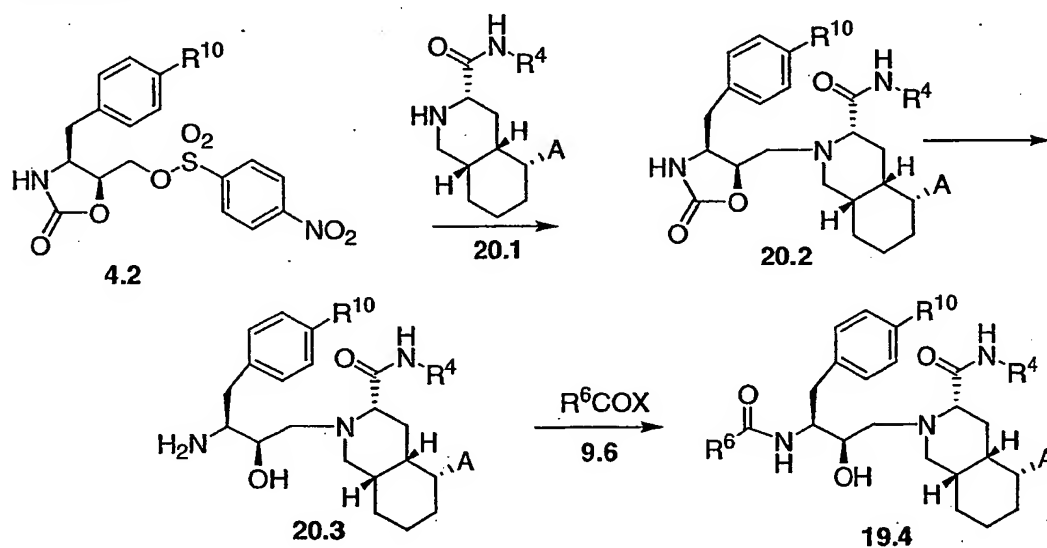
Schemes 22 and 23 depict the preparation of the phosphonate esters 4 in which X is sulfur. As shown in Scheme 22, the oxirane 7.7, prepared as described above (Scheme 7) is reacted with the decahydroisoquinoline derivative 19.1, in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. The reaction is conducted under the same conditions as described above for the preparation of the amine 7.8, (Scheme 7), to produce the hydroxyamine 22.1. The cbz protecting group present in the product 22.1 is then removed, using the same procedures as described above (Scheme 7) to afford the free amine 22.2. This material is then coupled with the carboxylic acid or activated derivative thereof, 9.6 to yield the amide 22.3. The coupling reaction is preformed under the same conditions as previously described.

The procedures illustrated in Scheme 22 depict the preparation of the compounds 22.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 23 illustrates the conversion of compounds 22.3 in which A is a precursor to the group $\text{link-P(O)(OR}^1\text{)}_2$ into the compounds 4. Procedures for
5 the conversion of the substituent A into the group $\text{link-P(O)(OR}^1\text{)}_2$ are illustrated below, (Schemes 24 - 69).

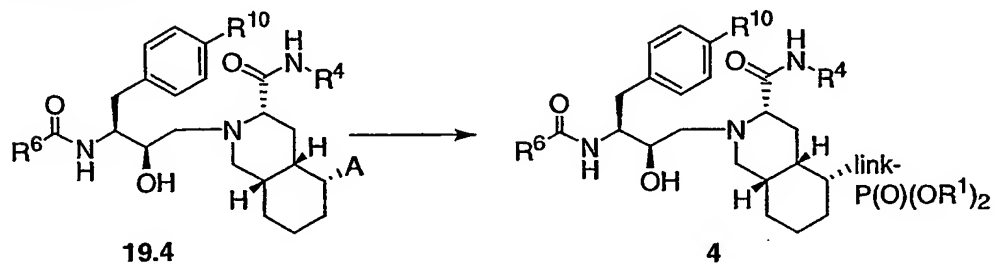
Scheme 19



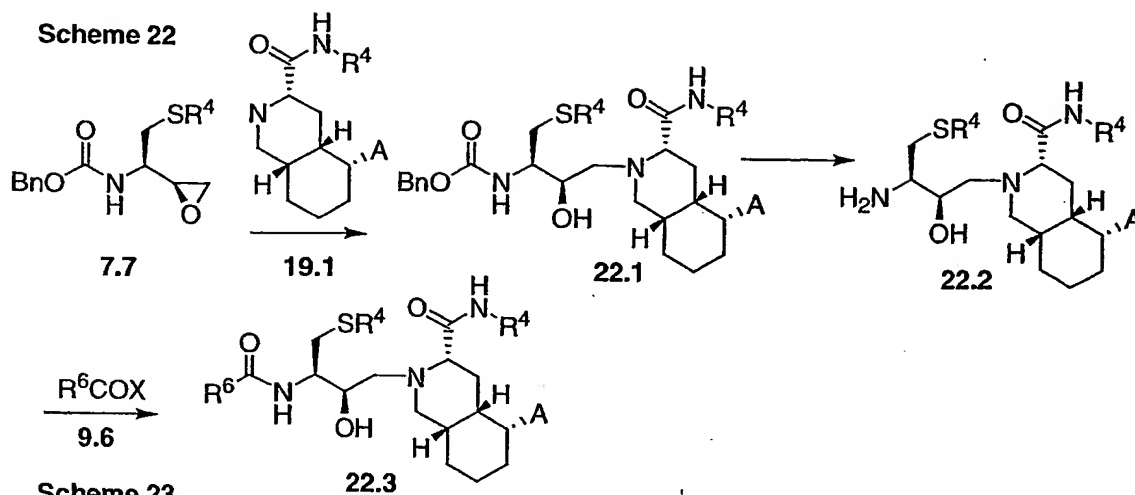
Scheme 20



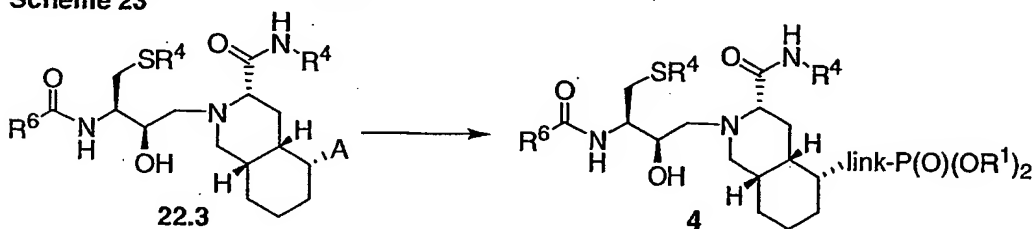
Scheme 21



Scheme 22

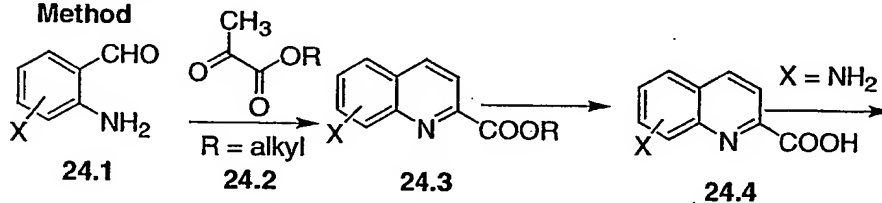
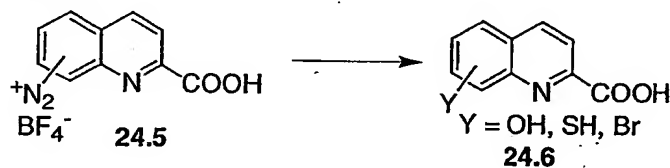


Scheme 23

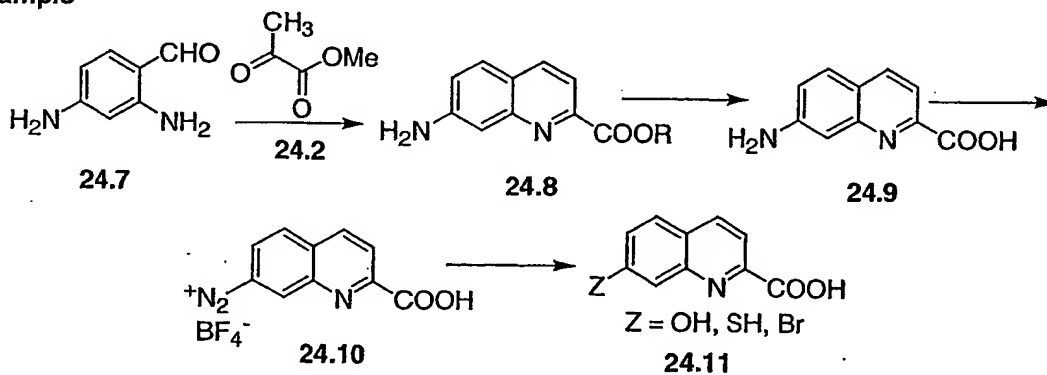


Scheme 24

Method

X = OH, SH, NH₂, Br

Example



Preparation of quinoline 2-carboxylic acids 1.7 incorporating phosphonate moieties or precursors thereto.

- 5 The reaction sequence depicted in Scheme 1 requires the use of a quinoline-2-carboxylic acid reactant 1.7 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br.

A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino
10 and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het. Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines
15 is described, for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p. 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

- 20 Scheme 24 illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde 24.1 is reacted with an alkyl pyruvate ester 24.2, in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester 24.3. Hydrolysis of the ester, for example by the use of aqueous base, then
25 afford the corresponding carboxylic acid 24.4. The carboxylic acid product 24.4 in which X is NH₂ can be further transformed into the corresponding compounds 24.6 in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner,
30 H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium

tetrafluoroborate, is then heated in aqueous solution, for example as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol **24.6**, X = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, **24.6**, Y = Br. Alternatively, the diazonium tetrafluoroborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 200, 24, 123, to afford the thiol **24.6**, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters **24.3** instead of the carboxylic acids **24.5**.

For example, 2,4-diaminobenzaldehyde **24.7** (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate **24.2** in methanol, in the presence of a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate **24.8**. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **24.9**. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoroborate **24.10** by reaction with sodium nitrite and tetrafluoroboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, **24.11**, Z = OH. Alternatively, the diazonium tetrafluoroborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-bromoquinoline-2-carboxylic acid **24.11**, X = Br. Alternatively, the diazonium tetrafluoroborate **24.10** is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid **24.11**, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde **24.7**, different aminobenzaldehydes **24.1**, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids **24.6** are obtained. The variously substituted quinoline carboxylic acids and esters can then be transformed, as described below, (Schemes 25 – 27) into phosphonate-containing derivatives.

Scheme 25 depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester **25.1** is transformed, via a

diazotization procedure as described above (Scheme 24) into the corresponding phenol or thiol 25.2. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate 25.3, under the conditions of the Mitsunobu reaction, to afford the phosphonate ester 25.4. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the thioether products 25.5. Basic hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid 25.6. For example, methyl 6-amino-2-quinoline carboxylate 25.7, prepared as described in J. Het. Chem., 1989, 26, 929, is converted, by means of the diazotization procedure described above, into methyl 6-mercaptoquinoline-2-carboxylate 25.8. This material is reacted with a dialkyl hydroxymethylphosphonate 25.9 (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether 25.10. Basic hydrolysis then afford the carboxylic acid 25.11. Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline carboxylate 25.7, different aminoquinoline carboxylic esters 25.1, and/or different dialkyl hydroxymethylphosphonates 25.9 the corresponding phosphonate ester products 25.3 are obtained.

Scheme 26 illustrates the preparation of quinoline-2-carboxylic acids incorporating phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester 26.1 is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate 26.2. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate.

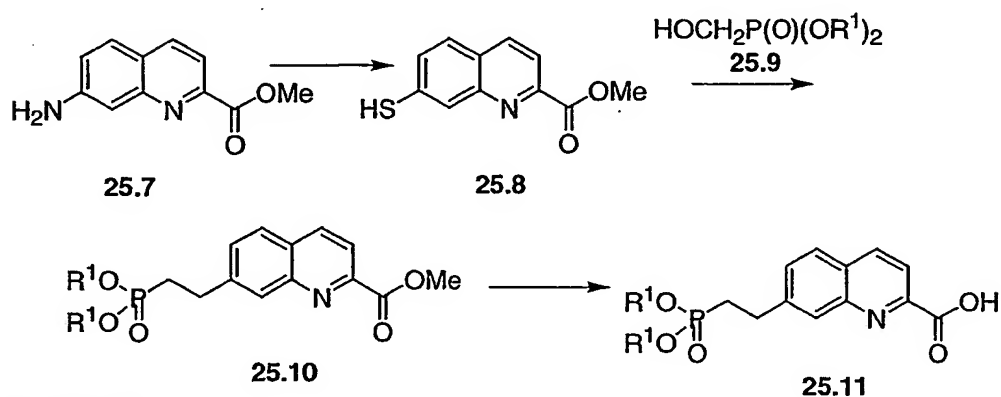
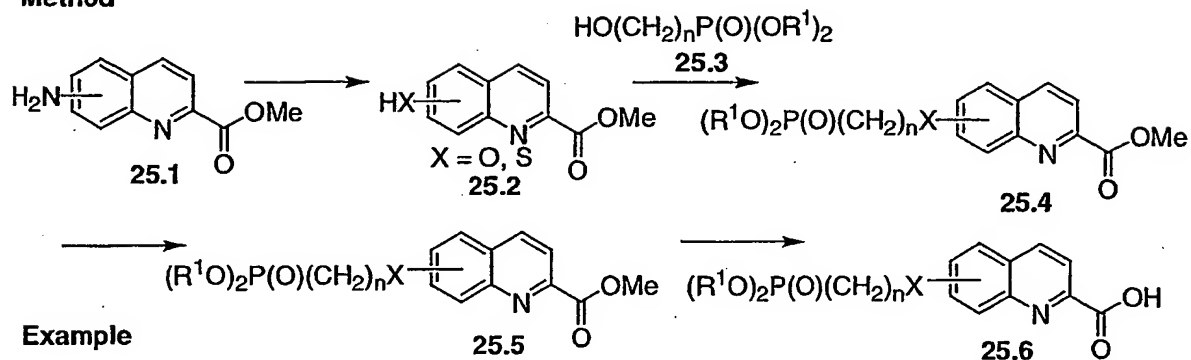
- Thus, Heck coupling of the bromo compound 26.1 and the olefin 26.2 affords the olefinic ester 26.3. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid 26.4. Optionally, the unsaturated carboxylic acid 26.4 can be reduced to afford the saturated analog 26.5. The
- 5 reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5. For example, methyl 7-bromoquinoline-2-carboxylate, 26.6, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60°C with a
- 10 dialkyl vinylphosphonate 26.7 (Aldrich) in the presence of 2 mol% of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product 26.8. The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid 26.9. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product 26.10.
- 15 Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate 26.6, different bromoquinoline carboxylic esters 26.1, and/or different dialkyl alkenylphosphonates 26.2, the corresponding phosphonate ester products 26.4 and 26.5 are obtained.
- 20 Scheme 27 depicts the preparation of quinoline-2-carboxylic acids 27.5 in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate 27.1 is reacted with a phosphonate aldehyde 27.2 under reductive amination conditions, to afford the aminoalkyl product 27.3. The preparation of amines by means of reductive amination procedures is described, for
- 25 example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in
- 30 the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product 27.4 is then hydrolyzed to yield the free carboxylic acid 27.5.

For example, methyl 7-aminoquinoline-2-carboxylate **27.6**, prepared as described in J. Amer. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **27.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **27.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **27.9**.

- 5 Using the above procedures, but employing, in place of the formylmethyl phosphonate **27.2**, different formylalkyl phosphonates, and/or different aminoquinolines **27.1**, the corresponding products **27.5** are obtained.

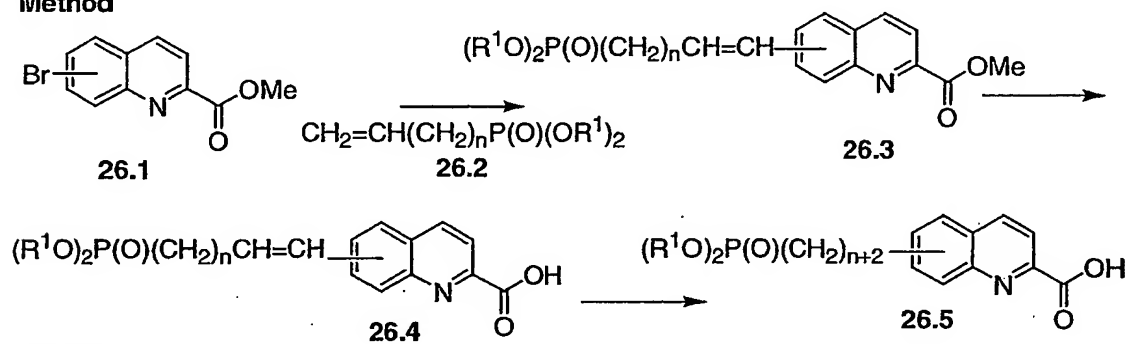
Scheme 25

Method

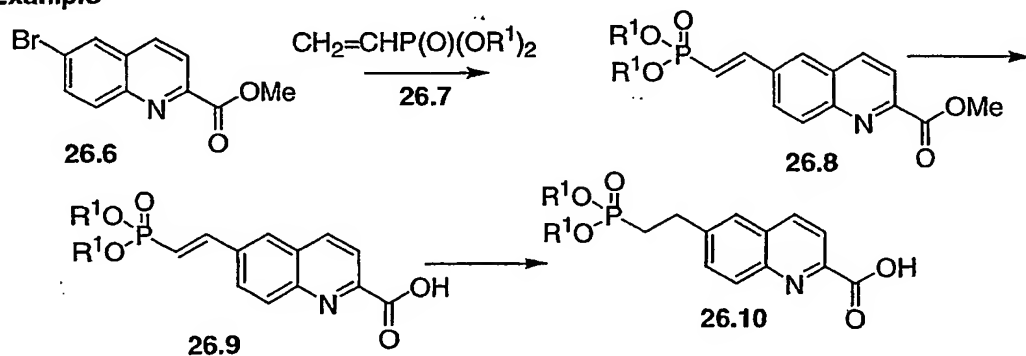


Scheme 26

Method

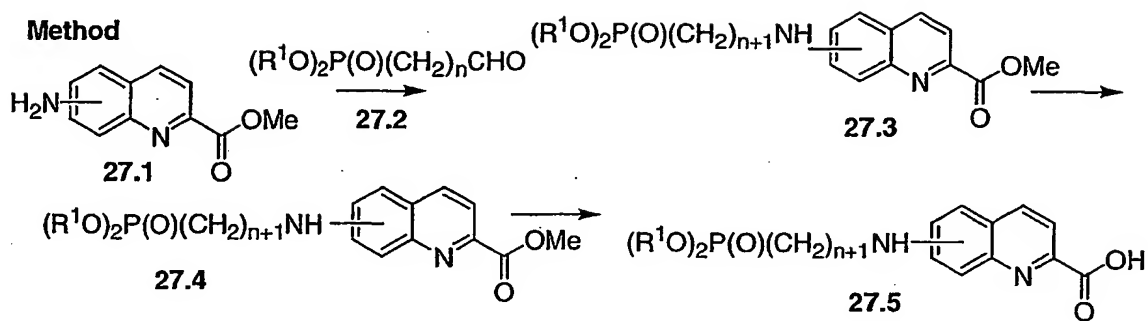


Example

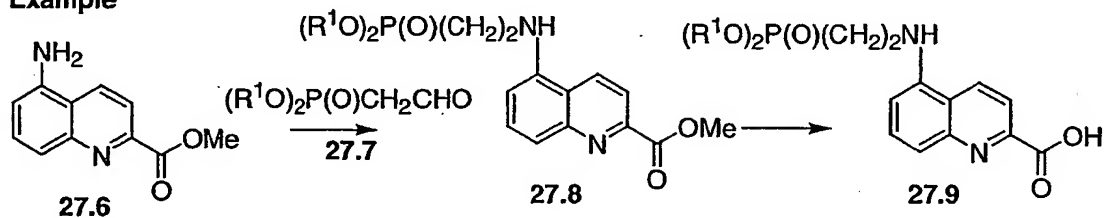


Scheme 27

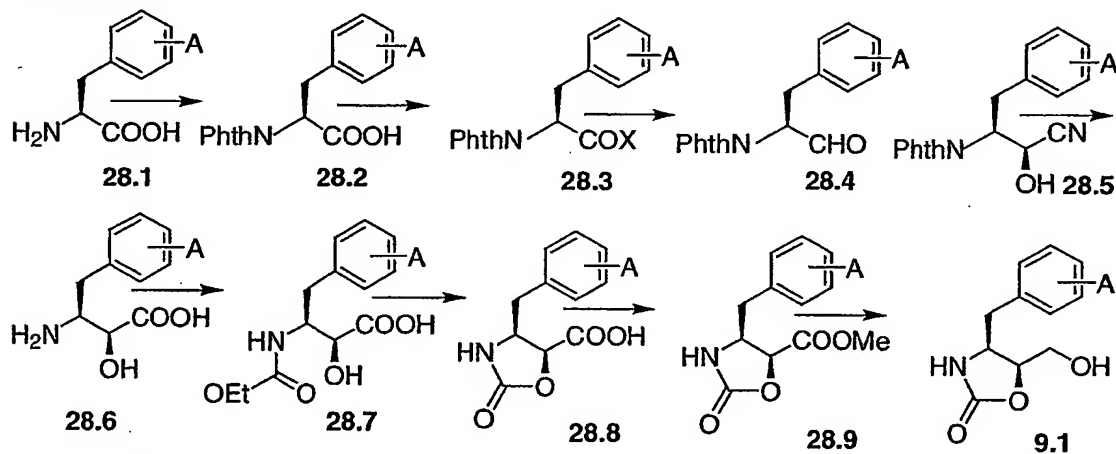
Method



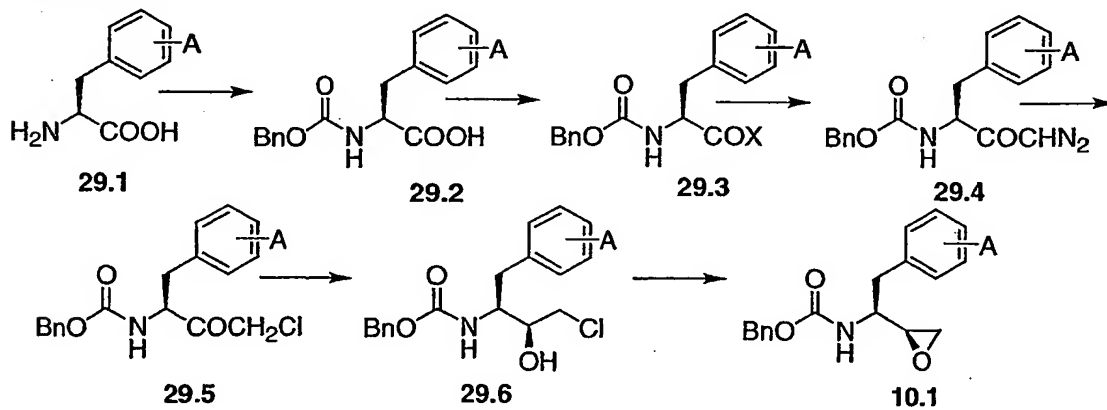
Example



Scheme 28



Scheme 29



Preparation of phenylalanine derivatives 9.1 and 10.1 incorporating phosphonate moieties or precursors thereto.

5 Scheme 28 illustrates the preparation of the hydroxymethyl oxazolidine derivative 9.1, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br. In this reaction sequence, the substituted phenylalanine 28.1, in which A is as defined above, is transformed, via the intermediates 28.2-28.9, into the hydroxymethyl product 9.1. The reaction conditions for each step in the sequence are the same as those described
10 above for the corresponding step shown in Scheme 5. The conversion of the substituent A into the group link-P(O)(OR¹)₂ may be effected at any convenient step in the reaction sequence, or after the reactant 9.1 has been incorporated into the intermediates 9.5 (Scheme 9). Specific examples of the preparation of the hydroxymethyl oxazolidinone reactant 9.1 are shown below, (Schemes 30-31).

15 Scheme 29 illustrates the preparation of the oxirane intermediate 10.1, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br. In this reaction sequence, the substituted phenylalanine 29.1, in which A is as defined above, is transformed, via the intermediates 29.2-29.6, into the oxirane 10.1. The reaction conditions
20 for each step in the sequence are the same as those described above for the corresponding step shown in Scheme 2. The conversion of the substituent A into the group link-P(O)(OR¹)₂ may be effected at any convenient step in the reaction sequence, or after the reactant 10.1 has been incorporated into the intermediates 9.5 (Scheme 10). Specific examples of the preparation of the oxiranes reactant 10.1 are shown below, (Schemes 32-34).

25 Scheme 30 depicts the preparation of hydroxymethyloxazolidinones 30.9 in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine 30.1 is converted, using the series of reactions illustrated in Scheme 28, into the bromophenyloxazolidinone 30.2. The bromophenyl compound is then coupled, in
30 the presence of a palladium (0) catalyst, with a dialkyl phosphite 30.3, to afford the phosphonate product 30.4. The reaction between aryl bromide and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, 56, 1981, and in J. Med. Chem., 1992, 35, 1371.

The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°C, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The carbomethoxy substituent in the resultant phosphonate ester 30.4 is then reduced with sodium borohydride to the corresponding

5 hydroxymethyl derivative 30.5, using the procedure described above (Scheme 28)

For example, 3-bromophenylalanine 30.6, prepared as described in *Pept. Res.*, 1990, 3, 176, is converted, using the sequence of reactions shown in Scheme 28, into 4-(3-bromo-benzyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester 30.7. This compound is then coupled with a dialkyl phosphite 30.3, in toluene solution at reflux, in the presence of a catalytic amount of

10 tetrakis(triphenylphosphine)palladium(0) and triethylamine, to afford the phosphonate ester 30.8. The carbomethoxy substituent is then reduced with sodium borohydride, as described above, to afford the hydroxymethyl product 30.9.

Using the above procedures, but employing, in place of 3-bromophenylalanine 30.6 different bromophenylalanines 30.1 and/or different dialkyl phosphites 30.3, the corresponding products

15 30.5 are obtained.

Scheme 31 illustrates the preparation of phosphonate-containing hydroxymethyl oxazolidinones 31.9 and 31.12 in which the phosphonate group is attached by means of a heteroatom and a carbon chain. In this sequence of reactions, a hydroxy or thio-substituted

20 phenylalanine 31.1 is converted into the benzyl ester 31.2 by means of a conventional acid catalyzed esterification reaction. The hydroxyl or mercapto group is then protected. The protection of phenyl hydroxyl and thiol groups are described, respectively, in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as

25 trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction

30 between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in *Bull. Chem. Soc. Jpn.*, 37, 433, 1974. The protected ester 31.3 is then reacted with phthalic anhydride, as described above (Scheme 28) to afford the phthalimide 31.4. The

benzyl ester is then removed, for example by catalytic hydrogenation or by treatment with aqueous base, to afford the carboxylic acid **31.5**. This compound is transformed, by means of the series of reactions shown in Scheme 28, into the carbomethoxy oxazolidinone **31.6**, using in each step the same conditions as are described above (Scheme 28). The protected OH or SH group is then deprotected. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978. The resultant phenol or thiol **31.7** is then reacted with a hydroxyalkyl phosphonate **31.20** under the conditions of the Mitsunobu reaction, as described above (Scheme 25), to afford the ether or thioether **31.8**. The latter compound is then reduced with sodium borohydride, as described above (Scheme 28) to afford the hydroxymethyl analog **31.9**.

Alternatively, the phenol or thiophenol **31.7** is reacted with a dialkyl bromoalkyl phosphonate **31.10** to afford the alkylation product **31.11**. The alkylation reaction is preformed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, optionally in the presence of potassium iodide, and in the presence of an inorganic base such as potassium or cesium carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine. The ether or thioether product is then reduced with sodium borohydride to afford the hydroxymethyl compound **31.12**.

For example, 3-hydroxyphenylalanine **31.13** (Fluka) is converted in to the benzyl ester **31.14** by means of a conventional acid-catalyzed esterification reaction. The ester is then reacted with tert-butylchlorodimethylsilane and imidazole in dimethylformamide, to afford the silyl ether **31.15**. The protected ether is then reacted with phthalic anhydride, as described above (Scheme 28) to yield the phthalimido-protected compound **31.16**. Basic hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, then affords the carboxylic acid **31.17**. This compound is then transformed, by means of the series of reactions shown in Scheme 28, into the carbomethoxy-substituted oxazolidinone **31.18**. The silyl protecting group is then removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, to produce the phenol **31.19**. The latter compound is reacted with a

dialkyl hydroxymethyl phosphonate **31.20** diethylazodicarboxylate and triphenylphosphine, by means of the Mitsunobu reaction, as described above (Scheme 25) to yield the phenolic ether **31.21**. The carbomethoxy group is then reduced by reaction with sodium borohydride, as described above, to afford the carbinol **31.22**.

- 5 Using the above procedures, but employing, in place of 3-hydroxyphenylalanine **31.13**, different hydroxy or mercapto-substituted phenylalanines **31.1**, and/or different dialkyl hydroxyalkyl phosphonates **31.20**, the corresponding products **31.9** are obtained.
- As a further example of the methods illustrated in Scheme 31, 4-mercaptophenylalanine **31.23**, prepared as described in J. Amer. Chem. Soc., 1997, 119, 7173, is converted into the benzyl
- 10 ester **31.24** by means of a conventional acid-catalyzed esterification reaction. The mercapto group is then protected by conversion to the S-adamantyl group, by reaction with 1-adamantanol and trifluoroacetic acid at ambient temperature as described in Chem. Pharm. Bull., 26, 1576, 1978. The amino group is then converted into the phthalimido group as described above, and the ester moiety is hydrolyzed with aqueous base to afford the carboxylic
- 15 acid **31.27**. The latter compound is then transformed, by means of the series of reactions shown in Scheme 28, into the carbomethoxy oxazolidinone **31.28**. The adamantyl protecting group is then removed by treatment of the thioether **31.28** with mercuric acetate in trifluoroacetic acid at 0°C, as described in Chem. Pharm. Bull., 26, 1576, 1978, to produce the thiol **31.29**. The thiol is then reacted with one molar equivalent of a dialkyl
- 20 bromoethylphosphonate **31.30**, (Aldrich) and cesium carbonate in dimethylformamide at 70°C, to afford the thioether product **31.31**. The carbomethoxy group is then reduced with sodium borohydride, as described above, to prepare the carbinol **31.32**.
- Using the above procedures, but employing, in place of 4-mercaptophenylalanine **31.23**, different hydroxy or mercapto-substituted phenylalanines **31.10**, and/or different dialkyl
- 25 bromoalkyl phosphonates **31.10**, the corresponding products **31.12** are obtained.

- Scheme 32 illustrates the preparation of phenylalanine derivatives **32.3** in which the phosphonate group is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **32.1** is converted, by means of the series of reactions shown in
- 30 Scheme 29 into the oxirane **32.2**. This compound is then coupled with a dialkyl phosphite **30.3**, in the presence of a palladium(0) catalyst and an organic base, to afford the phosphonate

oxirane 32.3. The coupling reaction is performed under the same conditions previously described, (Scheme 30).

For example, 3-bromophenylalanine 32.4, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, into the oxirane 32.5. This compound is reacted, in toluene
5 solution at reflux temperature, with a dialkyl phosphonate 30.3, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine to afford the phosphonate ester 32.6.

Using the above procedures, but employing, in place of 4-bromophenylalanine 32.4, different bromo-substituted phenylalanines 32.1, and/or different dialkyl phosphites 30.3, the
10 corresponding products 32.3 are obtained.

Scheme 33 depicts the preparation of compounds 33.4 in which the phosphonate group is attached to the phenyl ring by means of a styrene moiety. In this reaction sequence, a vinyl-substituted phenylalanine 33.1 is converted, by means of the series of reactions shown in
15 Scheme 29, into the oxirane 33.2. This compound is then coupled with a dialkyl bromophenylphosphonate 33.3, employing the conditions of the Heck reaction, as described above (Scheme 26) to afford the coupled product 33.4.

For example, 4-vinylphenylalanine 33.5, prepared as described in EP 206460, is converted, as described above, into the oxirane 33.6. This compound is then coupled with a dialkyl 4-
20 bromophenylphosphonate 33.7, prepared as described in J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, to yield the phosphonate ester 33.8.

Using the above procedures, but employing, in place of 4-vinylphenylalanine 33.5, different vinyl-substituted phenylalanines 33.1, and/or different dialkyl bromophenylphosphonates 33.3,
25 the corresponding products 33.4 are obtained.

Scheme 34 depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom. In this procedure, a hydroxymethyl-substituted phenylalanine 34.1 is converted
30 into the cbz protected methyl ester 34.2, using the procedures described above (Scheme 29). The product 34.2 is then converted into a halomethyl-substituted compound 34.3. For example, the carbinol 34.2 is treated with triphenylphosphine and carbon tetrabromide, as

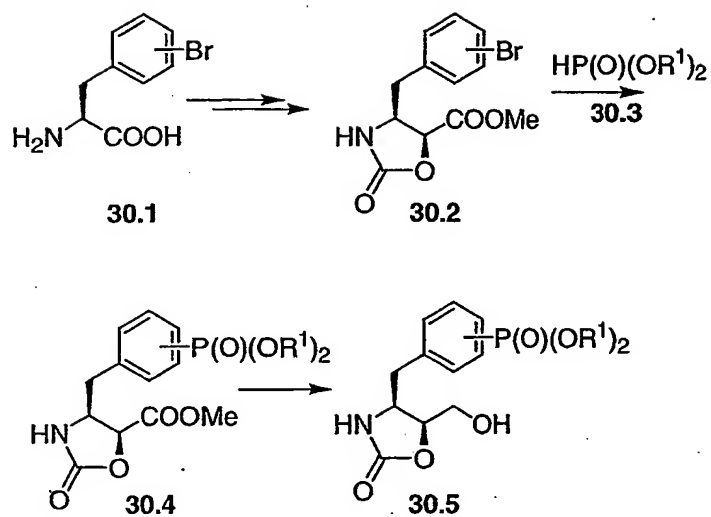
described in J. Amer. Chem. Soc., 108, 1035, 1986 to afford the product 34.3 in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate 34.4. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH₂ or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine, can be employed. If X is OH, a strong base such as lithium hexamethyldisilazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester 34.5, which is hydrolyzed to afford the carboxylic acid 34.6. The latter compound is then, by means of the sequence of reactions shown in Scheme 29, is transformed into the epoxide 34.7.

For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative 34.9, obtained from the 4-hydroxymethyl phenylalanine 34.8, the preparation of which is described in Syn. Comm., 1998, 28, 4279, is converted into the bromo derivative 34.10, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate 34.11, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product 34.12. The latter compound is then converted, using the sequence of reactions shown in Scheme 29, into the epoxide 34.14.

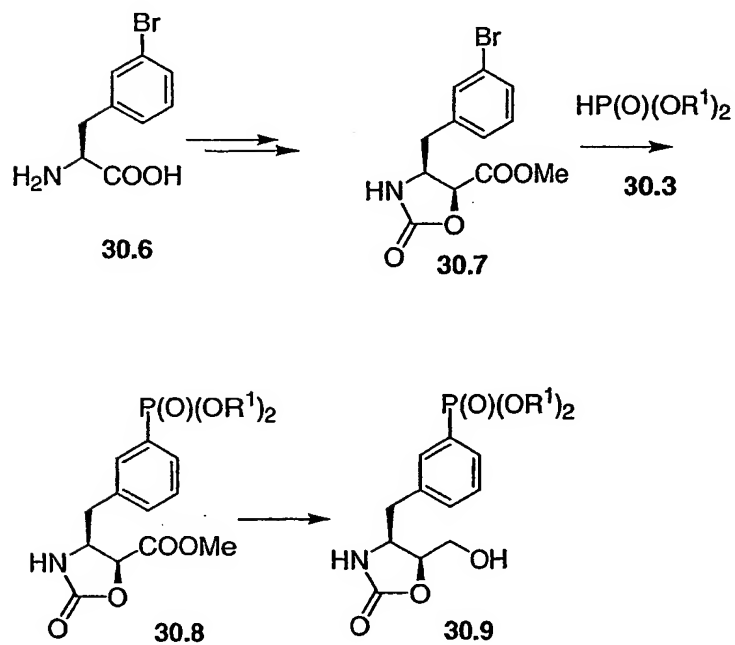
Using the above procedures, but employing different carbinols 34.1 in place of the carbinol 34.8, and/or different phosphonates 34.4, the corresponding products 34.7 are obtained.

Scheme 30

Method

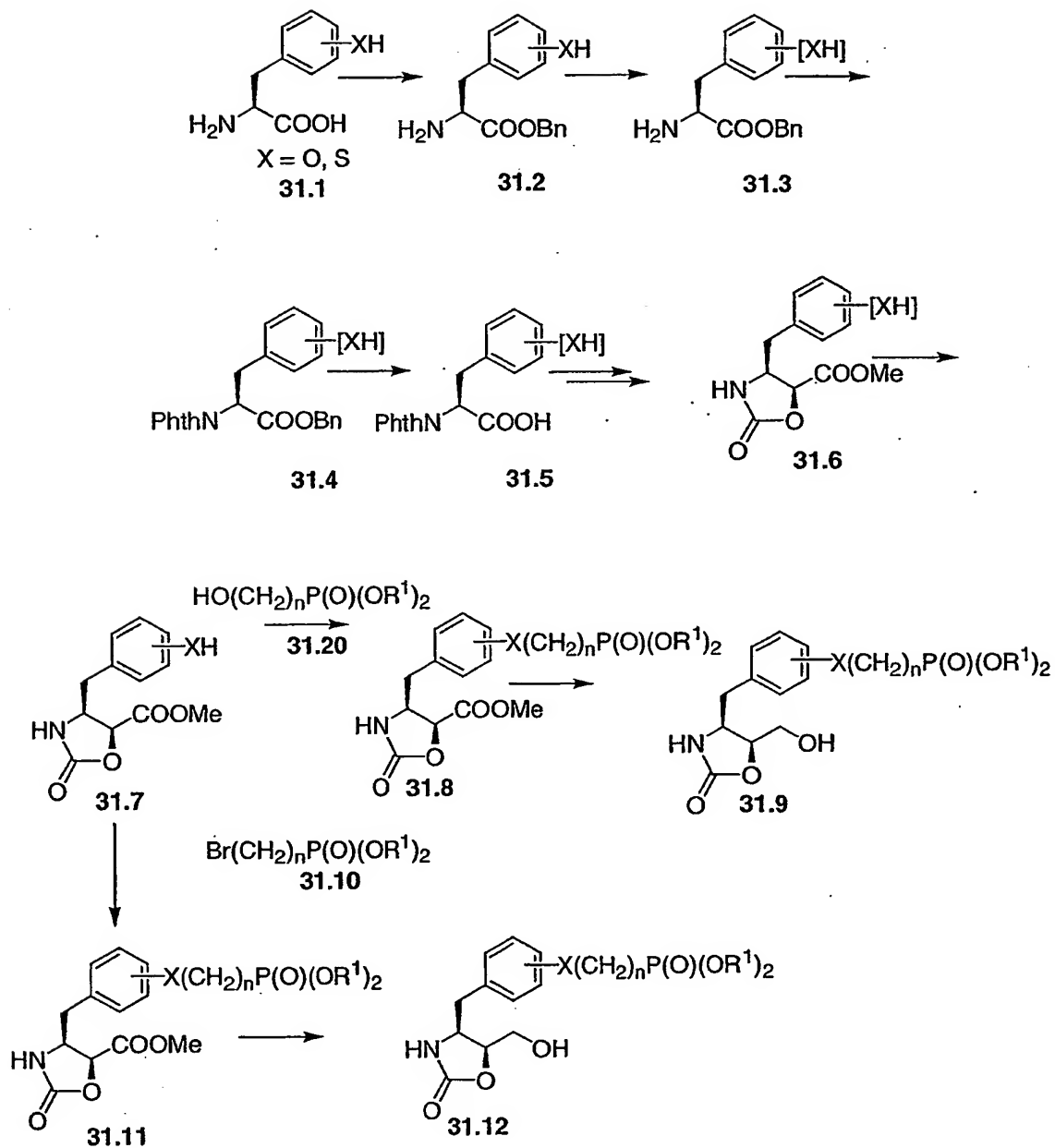


Example

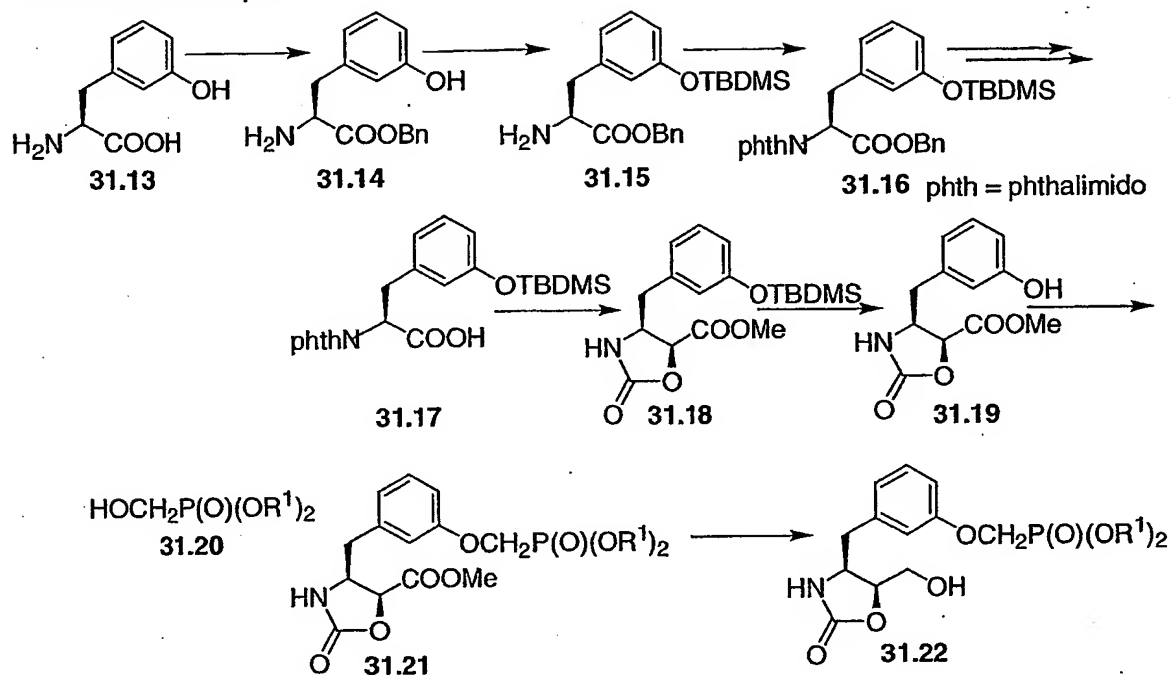


Scheme 31

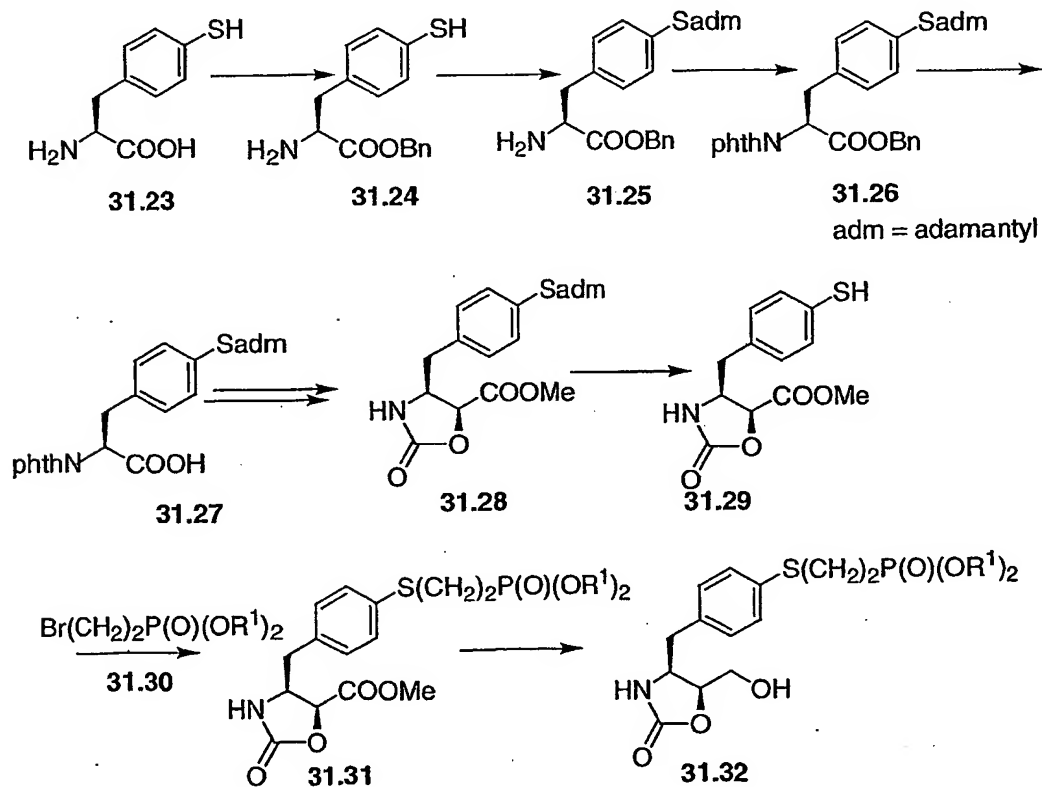
Method



Scheme 31 Example 1

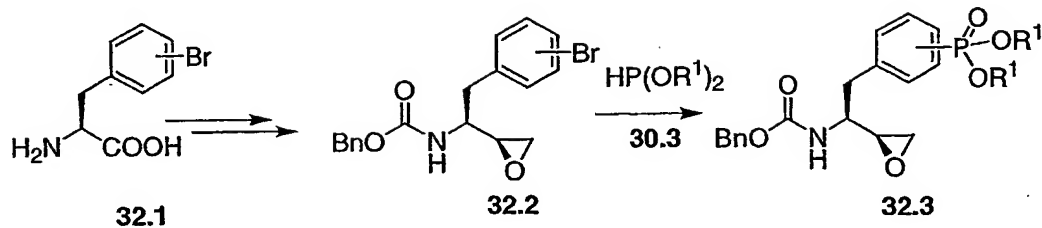


Scheme 31 Example 2

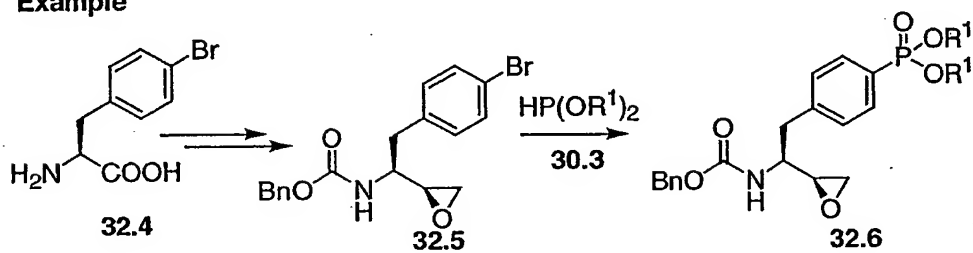


Scheme 32

Method

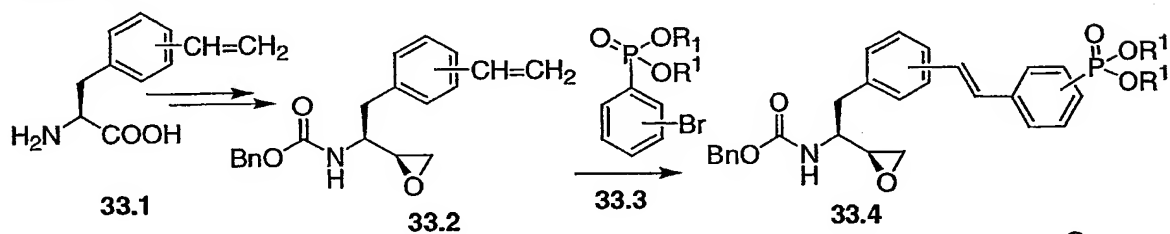


Example

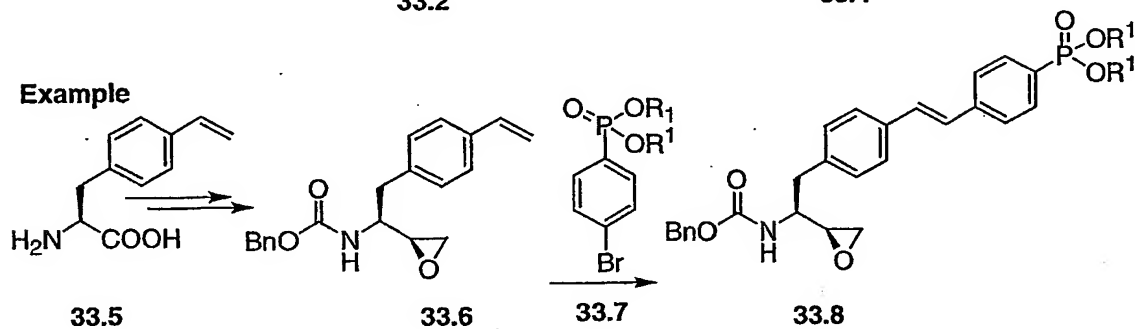


Scheme 33

Method

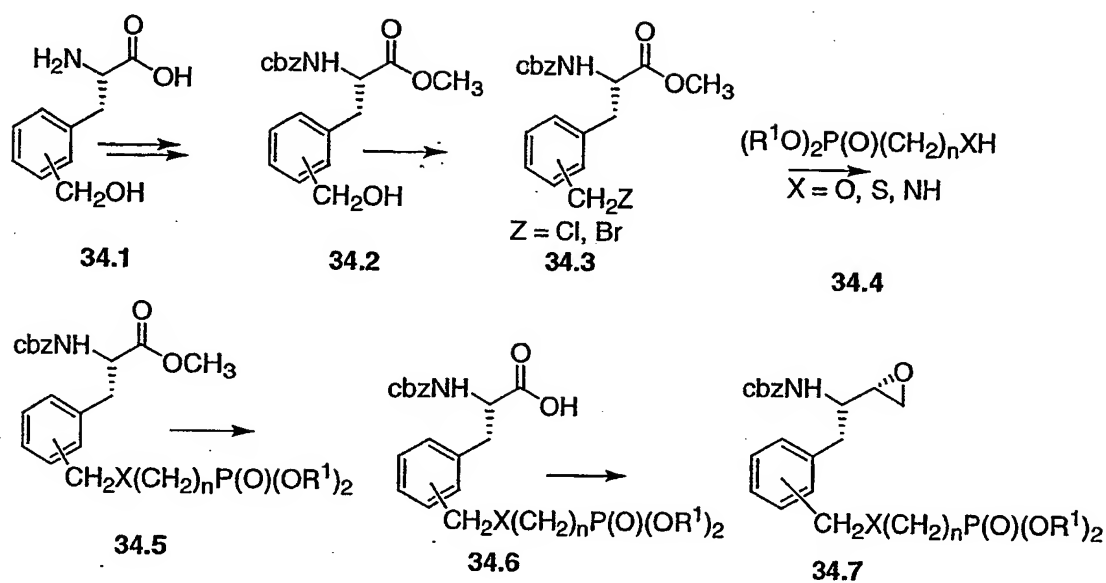


Example

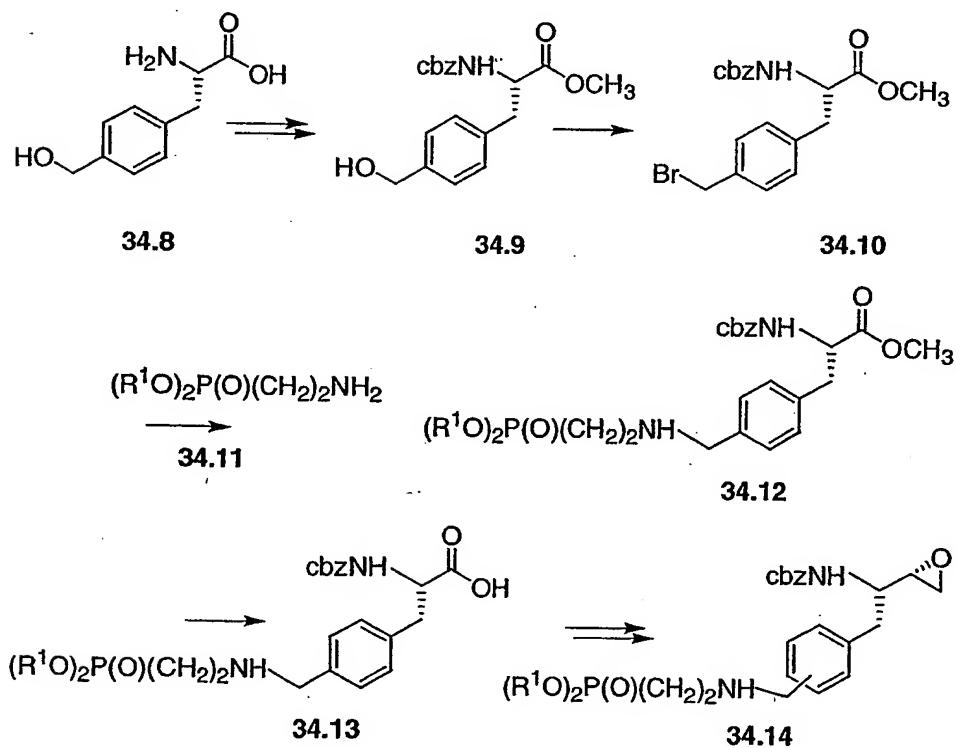


Scheme 34

Method



Example



Preparation of thiophenols 12.2 incorporating phosphonate groups.

Scheme 35 illustrates the preparation of thiophenols in which a phosphonate moiety is attached directly to the aromatic ring. In this procedure, a halo-substituted thiophenol 35.1 is subjected to a suitable protection procedure. The protection of thiophenols is described, for example, in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 277ff. The protected compound 35.2 is then coupled, under the influence of a transition metal catalyst, with a dialkyl phosphite 30.3, to afford the product 35.3. The product is then deprotected to afford the free thiophenol 35.4. Suitable protecting groups for this procedure include alkyl groups such as triphenylmethyl and the like. Palladium (0) catalysts are employed, and the reaction is conducted in an inert solvent such as benzene, toluene and the like, as described in *J. Med. Chem.*, 35, 1371, 1992. Preferably, the 3-bromothiophenol 35.5 is protected by conversion to the 9-fluorenylmethyl derivative 35.6, as described in *Protective Groups in Organic Synthesis*, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 284, and the product is reacted in toluene with a dialkyl phosphite in the presence of tetrakis(triphenylphosphine)palladium (0) and triethylamine, to yield the product 35.7. Deprotection, for example by treatment with aqueous ammonia in the presence of an organic co-solvent, as described in *J. Chem. Soc. Chem. Comm.* 1501, 1986, then gives the thiol 35.8.

Using the above procedures, but employing, in place of the bromo compound 35.5, different bromo compounds 35.2, and/or different phosphonates 30.3, there are obtained the corresponding thiols 35.4.

Scheme 36 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol 36.2 is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative 36.3. The latter compound is reacted with a halodialkyl phosphate 36.4, followed by deprotection as described previously, to afford the product 36.5.

For example, 4-bromothiophenol 36.7 is converted into the S-triphenylmethyl (trityl) derivative 36.8, as described in *Protective Groups in Organic Synthesis*, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative 36.9

- by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorodiethyl phosphite 36.10 to afford the phosphonate 36.11. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol 36.12.
- 5 Using the above procedures, but employing, in place of the bromo compound 36.7, different halo compounds 36.2, and/or different halo dialkyl phosphites 36.4, there are obtained the corresponding thiols 36.6.

- Scheme 37 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol 37.1 is subjected to free-radical bromination to afford a bromomethyl product 37.1a. This compound is reacted with a sodium dialkyl phosphite 37.2 or a trialkyl phosphite, to give the displacement or rearrangement product 37.3, which upon deprotection affords the thiophenols 37.4.
- 10
- 15 For example, 2-methylthiophenol 37.5 is protected by conversion to the benzoyl derivative 37.6, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product 37.7. This material is reacted with a sodium dialkyl phosphite 37.2, as described in J. Med. Chem., 35, 1371, 1992, to afford the product 37.8.
- 20 Alternatively, the bromomethyl compound 37.7 can be converted into the phosphonate 37.8 by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound 37.7 is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100°C to produce the phosphonate 37.8. Deprotection of 37.8, for example by treatment with aqueous ammonia, as described in J. Amer. Chem. Soc.,
- 25 85, 1337, 1963, then affords the thiol 37.9.
- Using the above procedures, but employing, in place of the bromomethyl compound 37.7, different bromomethyl compounds 37.2, there are obtained the corresponding thiols 37.4.

- Scheme 38 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol 38.1 is reacted with a dialkyl hydroxyalkylphosphonate 38.2 under the conditions of the Mitsunobu reaction, for example as described in Org. React., 1992, 42,
- 30

335, to afford the coupled product 38.3. Deprotection then yields the O- or S-linked products 38.4.

For example, the substrate 3-hydroxythiophenol, 38.5, is converted into the monotrityl ether 38.6, by reaction with one equivalent of trityl chloride, as described above. This compound is
5 reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate 38.7 in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound 38.8. Removal of the trityl protecting group, as described above, then affords the thiophenol 38.9.

Using the above procedures, but employing, in place of the phenol 38.5, different phenols or
10 thiophenols 38.1, and /or different phosphonates 38.2, there are obtained the corresponding thiols 38.4.

Scheme 39 illustrates the preparation of thiophenols 39.4 bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol 39.1 is reacted with an activated ester, for example the
15 trifluoromethanesulfonate 39.2, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product 39.3. Deprotection then affords the thiol 39.4.

For example, 4-methylaminothiophenol 39.5, is reacted with one equivalent of acetyl chloride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the product 39.6. This material is then reacted with, for
20 example, a dialkyl trifluoromethanesulfonylmethyl phosphonate 39.7, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product 39.8. Preferably, equimolar amounts of the phosphonate 39.7 and the amine 39.6 are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product 39.8. Deprotection, for example by
25 treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiophenol 39.9.

Using the above procedures, but employing, in place of the thioamine 39.5, different phenols, thiophenols or amines 39.1, and/or different phosphonates 39.2, there are obtained the corresponding products 39.4.

30 Scheme 40 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate 40.2. In this procedure, a suitably protected

hydroxy, thio or amino substituted thiophenol 40.1 is reacted with a dialkyl bromoalkyl phosphonate 40.2 to afford the product 40.3. Deprotection then affords the free thiophenol 40.4.

For example, 3-hydroxythiophenol 40.5 is converted into the S-trityl compound 40.6, as
5 described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate 40.7, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°C to yield the ether product 40.8. Deprotection, as described
10 above, then affords the thiol 40.9.

Using the above procedures, but employing, in place of the phenol 40.5, different phenols, thiophenols or amines 40.1, and/or different phosphonates 40.2, there are obtained the corresponding products 40.4.

15 Scheme 41 depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 41.2 is coupled with an aromatic bromo compound 41.1. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate 41.4,
20 or the saturated analog 41.6.

For example, 3-bromothiophenol is converted into the S-Fm derivative 41.7, as described above, and this compound is reacted with diethyl 1-butenyl phosphonate 41.8, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med.
25 Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product 41.9. Deprotection, as described above, then affords the thiol 41.10.

Optionally, the initially formed unsaturated phosphonate 41.9 can be subjected to catalytic hydrogenation, using, for example, palladium on carbon as catalyst, to yield the saturated
30 product 41.11, which upon deprotection affords the thiol 41.12.

Using the above procedures, but employing, in place of the bromo compound 41.7, different bromo compounds 41.1, and/or different phosphonates 41.2, there are obtained the corresponding products 41.4 and 41.6

- 5 Scheme 42 illustrates the preparation of an aryl-linked phosphonate ester 42.4 by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid 42.1 is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for
10 example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product 42.3 which is deprotected to yield the thiol 42.4.

- For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation
15 with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate 42.5. This material is reacted with diethyl 4-bromophenylphosphonate 42.6, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product 42.7. Deprotection, for example by the use of
20 tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol 42.8.

Using the above procedures, but employing, in place of the boronate 42.5, different boronates 42.1, and/or different phosphonates 42.2, there are obtained the corresponding products 42.4.

- Scheme 43 depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or
25 heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol 43.1 is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate 43.2, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product 43.3 is then deprotected to afford the thiol 43.4. For example, 1,4-
30 dimercaptobenzene is converted into the monobenzoyl ester 43.5 by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol 43.5 is then reacted with, for example diethyl 4-(bromomethyl)phenylphosphonate, 43.6,

the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C. The thioether product 43.7 thus obtained is deprotected, as described above, to afford the thiol 43.8.

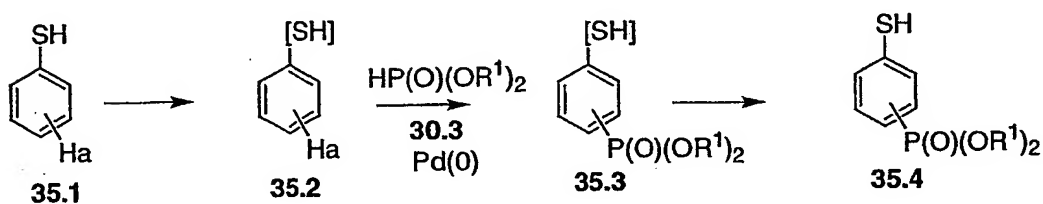
- 5 Using the above procedures, but employing, in place of the thiophenol 43.5, different phenols, thiophenols or amines 43.1, and/or different phosphonates 43.2, there are obtained the corresponding products 43.4.

- Scheme 44 illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.
- 10 In this procedure, a suitably protected thiophenol 44.1, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is $CH=CH$) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate 44.2, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide,
- 15 to afford the phosphonate ester 44.3. Deprotection, as described above, then affords the thiol 44.4. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation
- 20 of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by
- 25 diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p 707. For example, 2,3-dihydro-1H-indole-5-thiol, 44.5, the preparation of which is described in EP 209751, is converted into the benzoyl ester 44.6, as described above, and the ester is then
- 30 reacted with the triflate 44.7, using the conditions described above for the preparation of 39.8, (Scheme 39, to yield the phosphonate 44.8. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol 44.9.

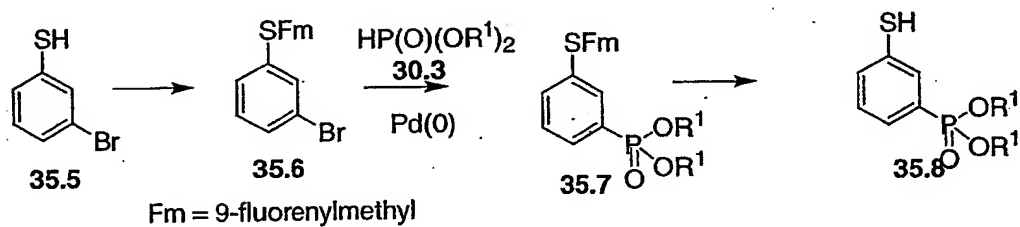
Using the above procedures, but employing, in place of the thiol 44.5, different thiols 44.1, and/or different triflates 44.2, there are obtained the corresponding products 44.4.

Scheme 35

Method

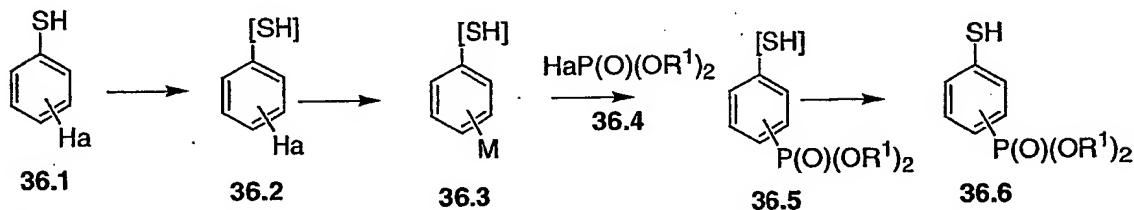


Example

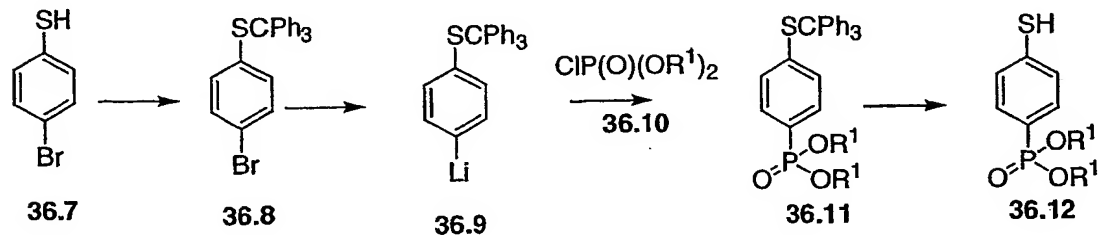


Scheme 36

Method

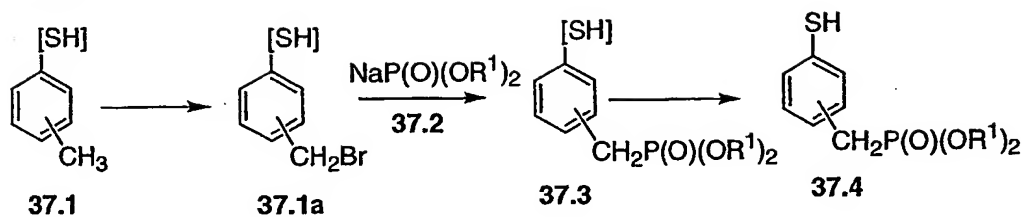


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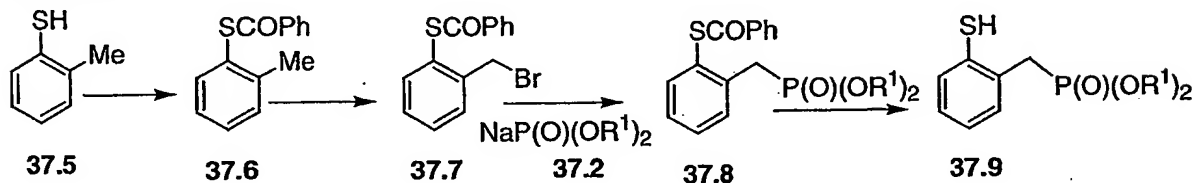


Scheme 37

Method

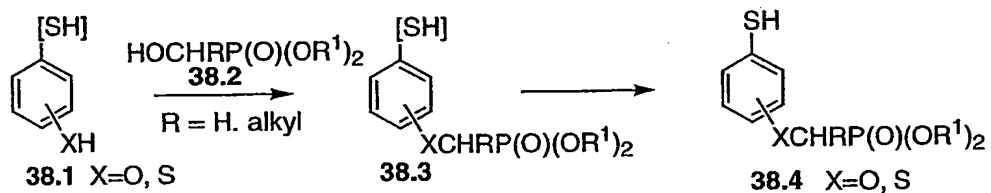


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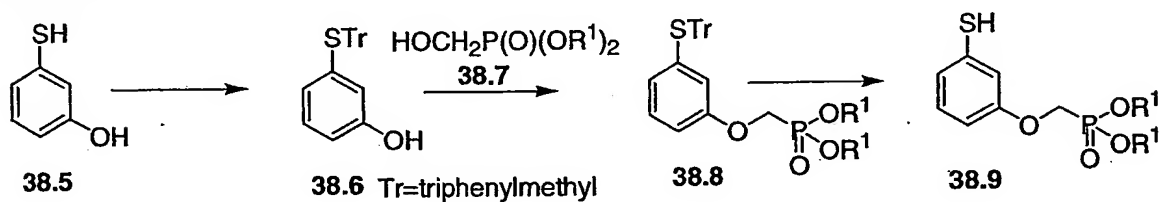


Scheme 38

Method

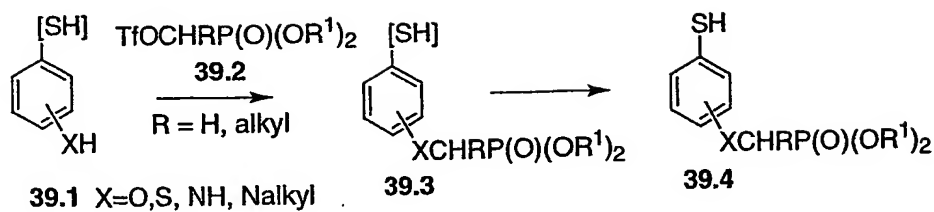


Example

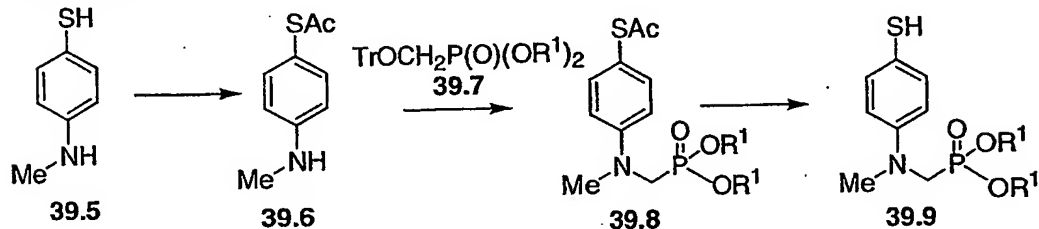


Scheme 39

Method

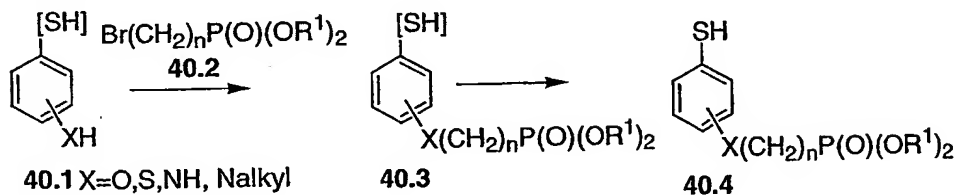


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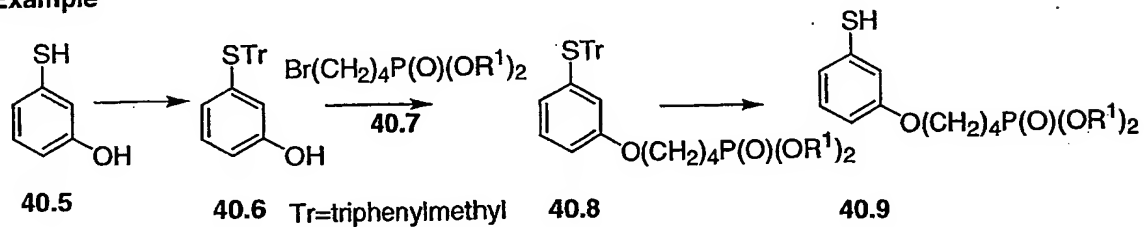


Scheme 40

Method

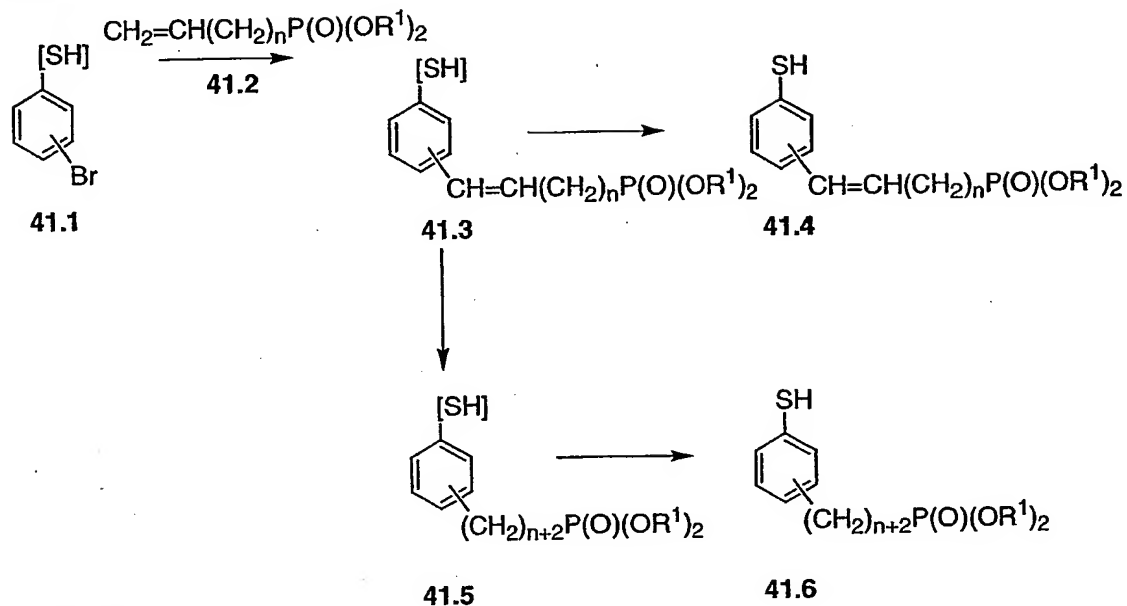


Example

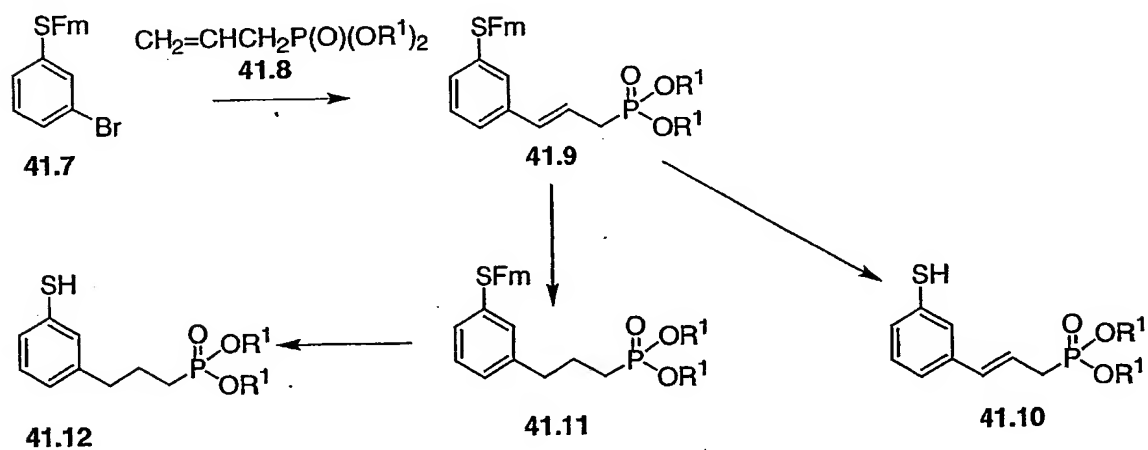


Scheme 41

Method

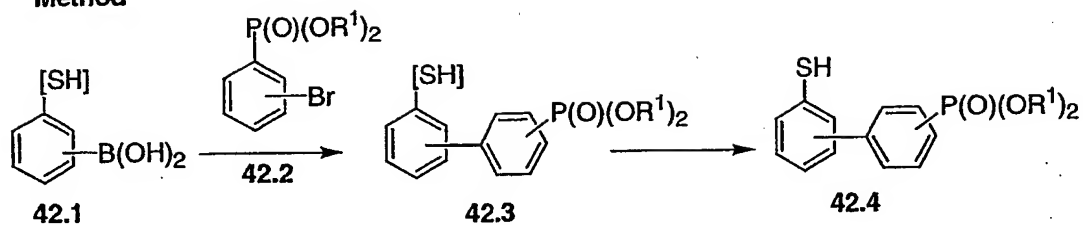


Example

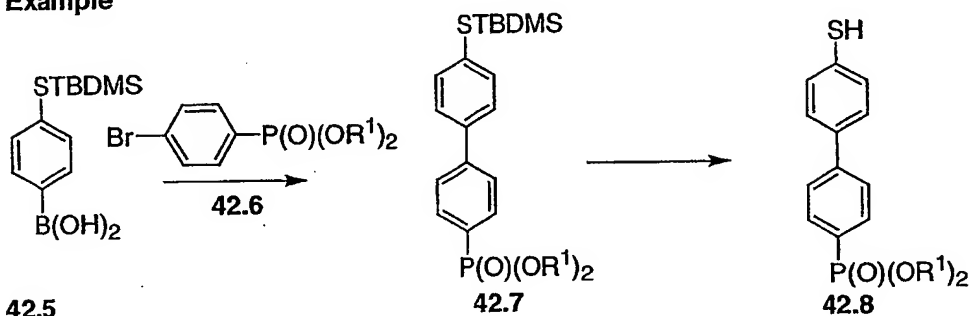


Scheme 42

Method



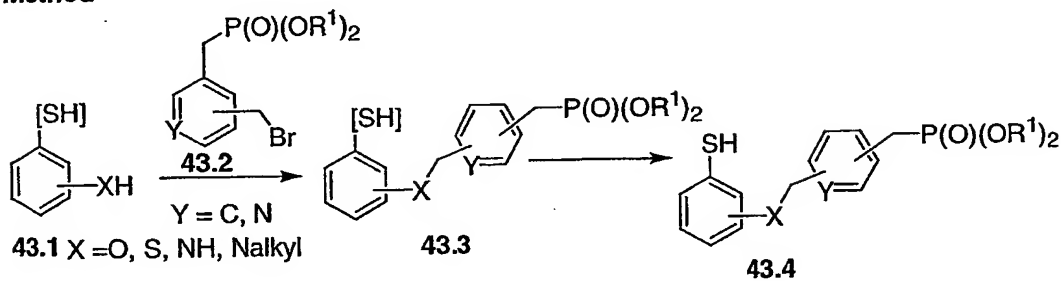
Example



42.5

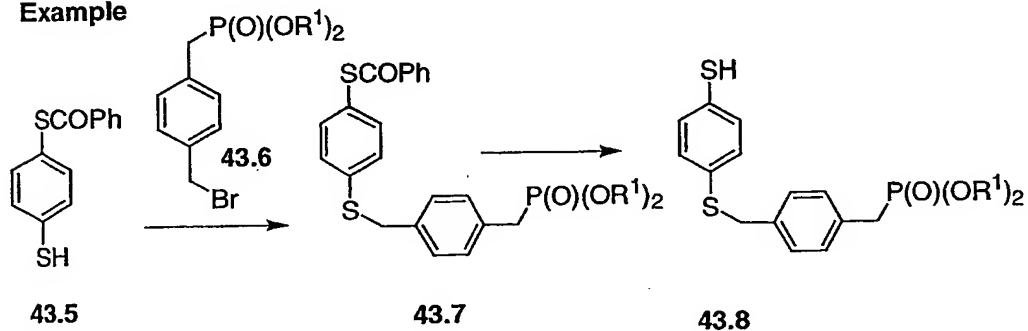
Scheme 43

Method



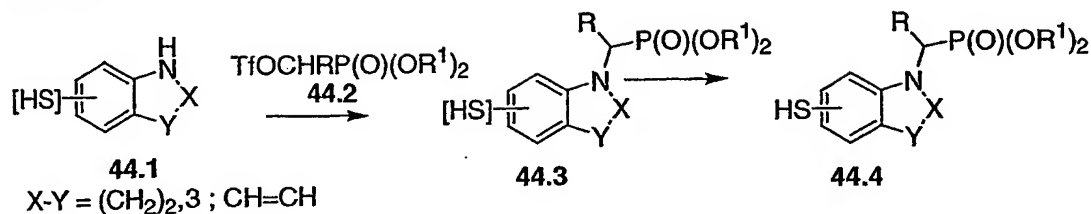
43.1 X = O, S, NH, Nalkyl

Example

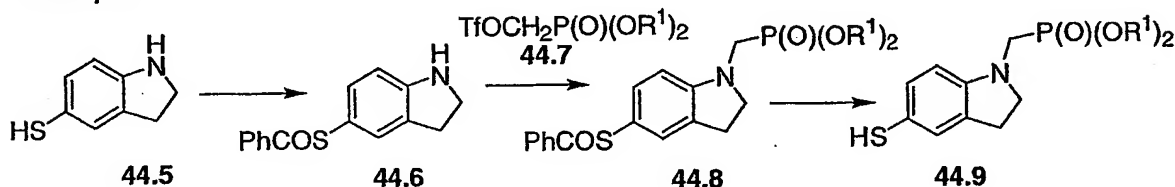


Scheme 44

Method



Example



Preparation of tert-butylamine derivatives incorporating phosphonate groups.

5

Scheme 45 describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2,2-dimethyl-2-aminoethyl bromide 45.1 is reacted with a trialkyl phosphite 45.2, under the conditions of the Arbuzov reaction, as described above, to afford the phosphonate 45.3, which is then deprotected as described previously to give 45.4

10

For example, the cbz derivative of 2,2-dimethyl-2-aminoethyl bromide 45.6, is heated with a trialkyl phosphite at ca 150°C to afford the product 45.7. Deprotection, as previously described, then affords the free amine 45.8.

Using the above procedures, but employing different trisubstituted phosphites, there are obtained the corresponding amines 45.4.

15

Scheme 46 illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain. An optionally protected alcohol or thiol 46.1 is reacted with a bromoalkylphosphonate 46.2, to afford the displacement product 46.3.

Deprotection, if needed, then yields the amine 46.4.

20

For example, the cbz derivative of 2-amino-2,2-dimethylethanol 46.5 is reacted with a dialkyl 4-bromobutyl phosphonate 46.6, prepared as described in Synthesis, 1994, 9, 909, in

dimethylformamide containing potassium carbonate and potassium iodide, at ca 60°C to afford the phosphonate 46.7 Deprotection then affords the free amine 46.8.

Using the above procedures, but employing different alcohols or thiols 46.1, and/or different bromoalkylphosphonates 46.2, there are obtained the corresponding products 46.4.

5

Scheme 47 describes the preparation of carbon-linked phosphonate tert butylamine derivatives, in which the carbon chain can be unsaturated or saturated.

In the procedure, a terminal acetylenic derivative of tert-butylamine 47.1 is reacted, under basic conditions, with a dialkyl chlorophosphite 47.2, as described above in the preparation of 10 36.5, (Scheme 36). The coupled product 47.3 is deprotected to afford the amine 47.4. Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products 47.5 and 47.6 respectively.

For example, 2-amino-2-methylprop-1-yne 47.7, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative 47.8, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and 15 P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide in tetrahydrofuran at -78°C. The resultant anion is then reacted with a dialkyl chlorophosphite 47.2 to afford the phosphonate 47.9. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine 47.10. Partial 20 catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p 566, produces the olefinic phosphonate 47.11, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate 47.12. 25 Using the above procedures, but employing different acetylenic amines 47.1, and/or different dialkyl halophosphites, there are obtained the corresponding products 47.4, 47.5 and 47.6.

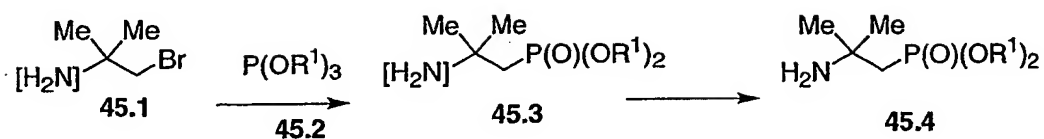
Scheme 48 illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

30 In this method, an aminoethyl-substituted cyclic amine 48.1 is reacted with a limited amount of a bromoalkyl phosphonate 48.2, using, for example, the conditions described above for the preparation of 40.3, (Scheme 40) to afford the displacement product 48.3.

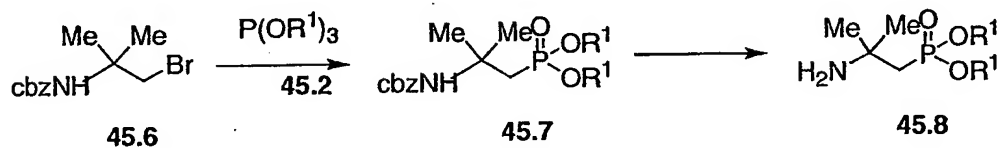
- For example, 3-(1-amino-1-methyl)ethylpyrrolidine **48.4**, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with a dialkyl 4-bromobutyl phosphonate **48.5**, prepared as described in Synthesis, 1994, 9, 909, to afford the displacement product **48.6**.
- 5 Using the above procedures, but employing different cyclic amines **48.1**, and/or different bromoalkylphosphonates **48.2**, there are obtained the corresponding products **48.3**.

Scheme 45

Method

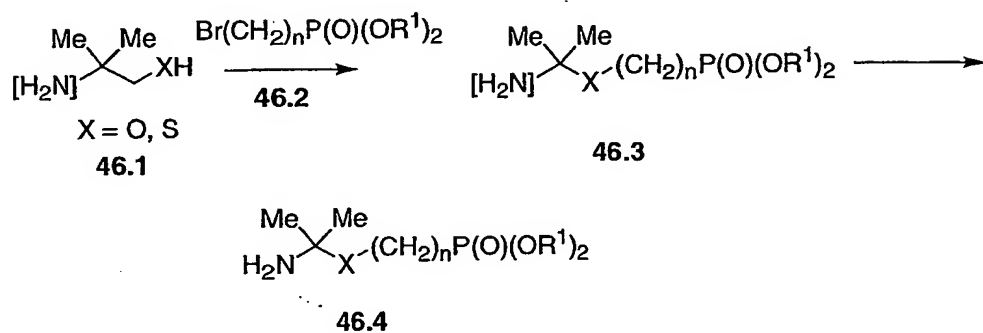


Example

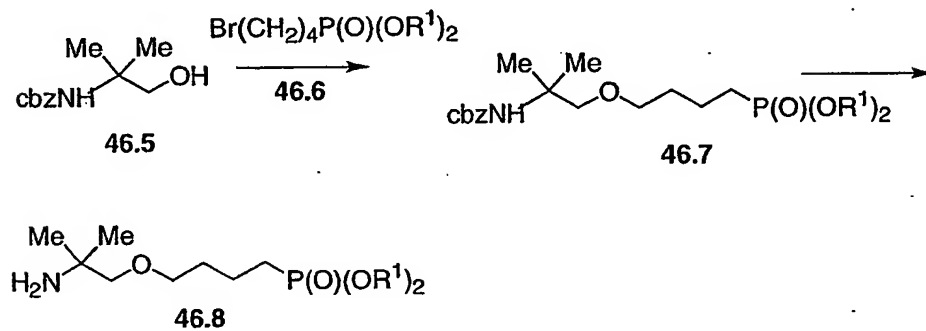


Scheme 46

Method

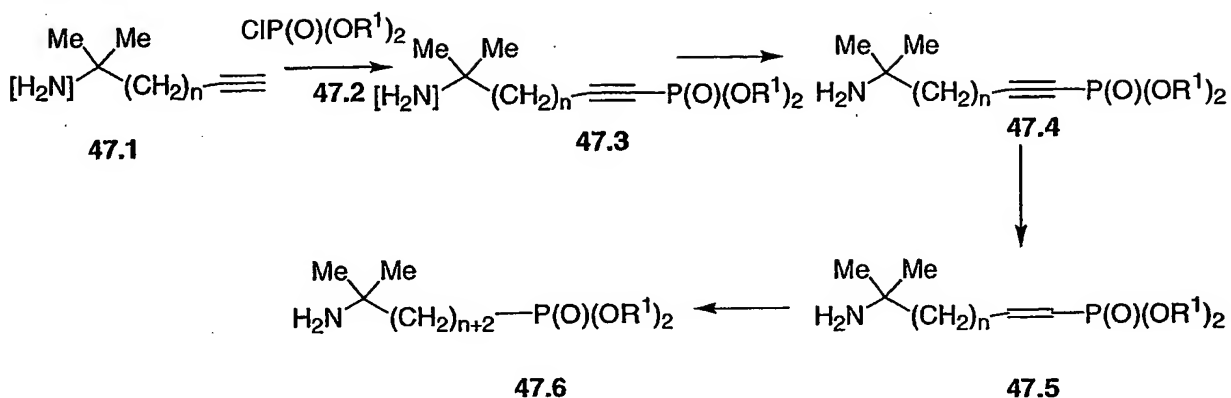


Example

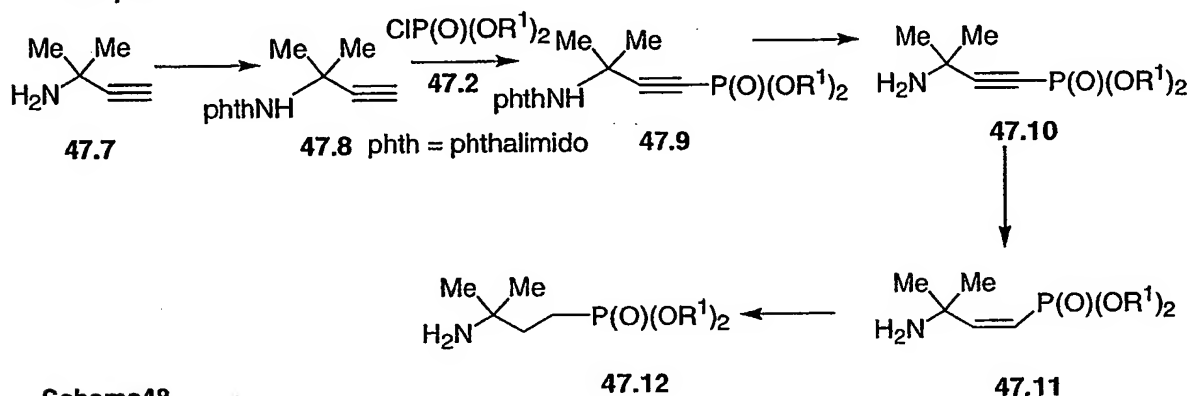


Scheme 47

Method

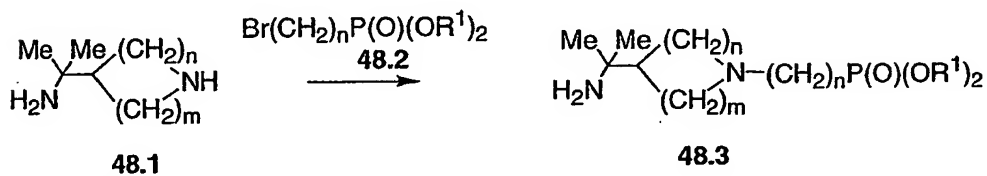


Example

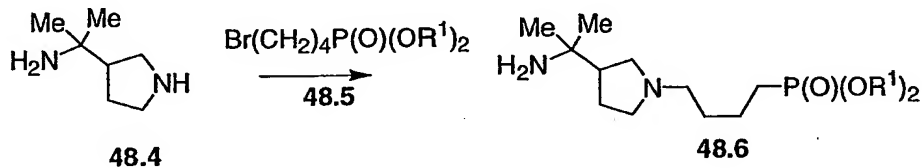


Scheme 48

Method



Example



Preparation of decahydroquinolines with phosphonate moieties at the 6-position.

Scheme 48a illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the intermediate 48a.4 are shown.

In the first route, 2-hydroxy-6-methylphenylalanine 48a.1, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative 48a.2. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product 48a.2, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product 48a.3. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound 48a.3 is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline 48a.4, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline 48a.4 can be obtained from 2-hydroxyphenylalanine 48a.5, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem. Rev., 1995, 95, 1797.

Typically, the substrate 48a.5 is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product 48a.4, in which R is H. Catalytic hydrogenation of the latter compound, using, for example, platinum as catalyst, as described in J. Amer. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-substituted decahydroisoquinoline 48a.6. The reduction can also be performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline 48a.4 is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°C, to afford the decahydroisoquinoline 48a.6.

Protection of the carboxyl and NH groups present in **48a.6** for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example,

5 pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **48a.9**, in which R is trichloroethyl and R₁ is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Amer. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butyl aluminum hydride, as described in J. Amer. Chem. Soc., 80, 5372, 1958, then affords the

10 alcohol **48a.10**.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as isopropanol, at ambient temperature, to afford the alcohol **48a.10**.

The alcohol **48a.6** can be converted into the thiol **48a.13** and the amine **48a.14**, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry. For

15 example, the alcohol **48a.6** can be converted into an activated ester such as the trifluoromethanesulfonyl ester or the methanesulfonate ester **48a.7**, by treatment with methanesulfonyl chloride and a base. The mesylate **48a.7** is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement

20 of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol **48a.13**.

For example, the mesylate **48a.7** is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **48a.12**, in which R is COCH₃. The product then treated with, a mild

25 base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol **48a.13**.

The mesylate **48a.7** can be treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p. 399, followed by deprotection as described previously,

30 to afford the amine **48a.14**.

For example, the mesylate **48a.7** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such

as, for example, dimethylformamide, at ambient temperature, to afford the displacement product 48a.8, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine 48a.14.

- 5 The application of the procedures described above for the conversion of the β -carbinol 48a.6 to the α -thiol 48a.13 and the α -amine 48a.14 can also be applied to the α -carbinol 48a.10, so as to afford the β -thiol and β -amine, 48a.11.

- Scheme 49 illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain.
- 10 In this procedure, an alcohol, thiol or amine 49.1 is reacted with a bromoalkyl phosphonate 49.2, under the conditions described above for the preparation of the phosphonate 40.3 (Scheme 40), to afford the displacement product 49.3. Removal of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below,
- 15 (Scheme 53) then yields the amine 49.8.

- For example, the compound 49.5, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, 49.6, the preparation of which is described in J.
- 20 Amer. Chem. Soc., 2000, 122, 1554 to afford the displacement product 49.7. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme 53) then yields the amine 49.8.

- Using the above procedures, but employing, in place of the α -thiol 49.5, the alcohols, thiols or amines 48a.6, 48a.10, 48a.11, 48a.13, 48a.14, of either α - or β -orientation, there are obtained
- 25 the corresponding products 49.4, in which the orientation of the side chain is the same as that of the O, N or S precursors.

- Scheme 50 illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by
- 30 means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p. 421.

In this procedure, the amines **48a.14** or **48a.11** are reacted with a phosphonate aldehyde **50.1**, in the presence of a reducing agent, to afford the alkylated amine **50.2**. Deprotection of the ester group, followed by conversion of the acid to the R⁴NH amide and N-deprotection, as described below, (Scheme 53) then yields the amine **50.3**.

- 5 For example, the protected amino compound **48a.14** is reacted with a dialkyl formylphosphonate **50.4**, the preparation of which is described in U.S. Patent 3,784,590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **50.5**. Deprotection of the ester group, followed by conversion of the acid to the R⁴NH amide and
- 10 N-deprotection, as described below, (Scheme 53) then yields the amine **50.6**. Using the above procedures, but employing, instead of the α -amine **48a.14**, the β isomer, **48a.11** and/or different aldehydes **50.1**, there are obtained the corresponding products **50.3**, in which the orientation of the side chain is the same as that of the amine precursor.

- 15 Scheme 51 depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain. In this procedure, a thiol phosphonate **51.2** is reacted with a mesylate **51.1**, to effect displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product **51.3**. Deprotection of the ester group, followed by conversion of the acid to the tert.
- 20 butyl amide and N-deprotection, as described below, (Scheme 53) then yields the amine **51.4**. For example, the protected mesylate **51.5** is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate **51.6**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the presence of a base such as, for example, potassium carbonate, at ambient temperature, to
- 25 afford the thio ether phosphonate **51.7**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 53) then yields the amine **51.8**. Using the above procedures, but employing, instead of the phosphonate **51.6**, different phosphonates **51.2**, there are obtained the corresponding products **51.4**.

30

Scheme 52 illustrates the preparation of decahydroisoquinoline phosphonates **52.4** in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The

compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates 52.1 and a bromomethyl substituted phosphonate 52.2. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant 52.1. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate can be employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is required. The displacement reaction affords the ether, thioether or amine compounds 52.3. Deprotection of the ester group, followed by conversion of the acid to the R⁴NH amide and N-deprotection, as described below, (Scheme 53) then yields the amine 52.4.

For example, the protected alcohol 52.5 is reacted at ambient temperature with a dialkyl 3-bromomethyl phenylmethylphosphonate 52.6, the preparation of which is described above, (Scheme 43). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a strong base, such as, for example, lithium hexamethyldisilylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate 52.6, to afford the product 52.7. Deprotection of the ester group, followed by conversion of the acid to the R⁴NH amide and N-deprotection, as described below, (Scheme 53) then yields the amine 52.8.

Using the above procedures, but employing, instead of the β-carbinol 52.5, different carbinols, thiols or amines 52.1, of either α- or β-orientation, and/or different phosphonates 52.2, in place of the phosphonate 52.6, there are obtained the corresponding products 52.4 in which the orientation of the side-chain is the same as that of the starting material 52.1.

Schemes 49-52 illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

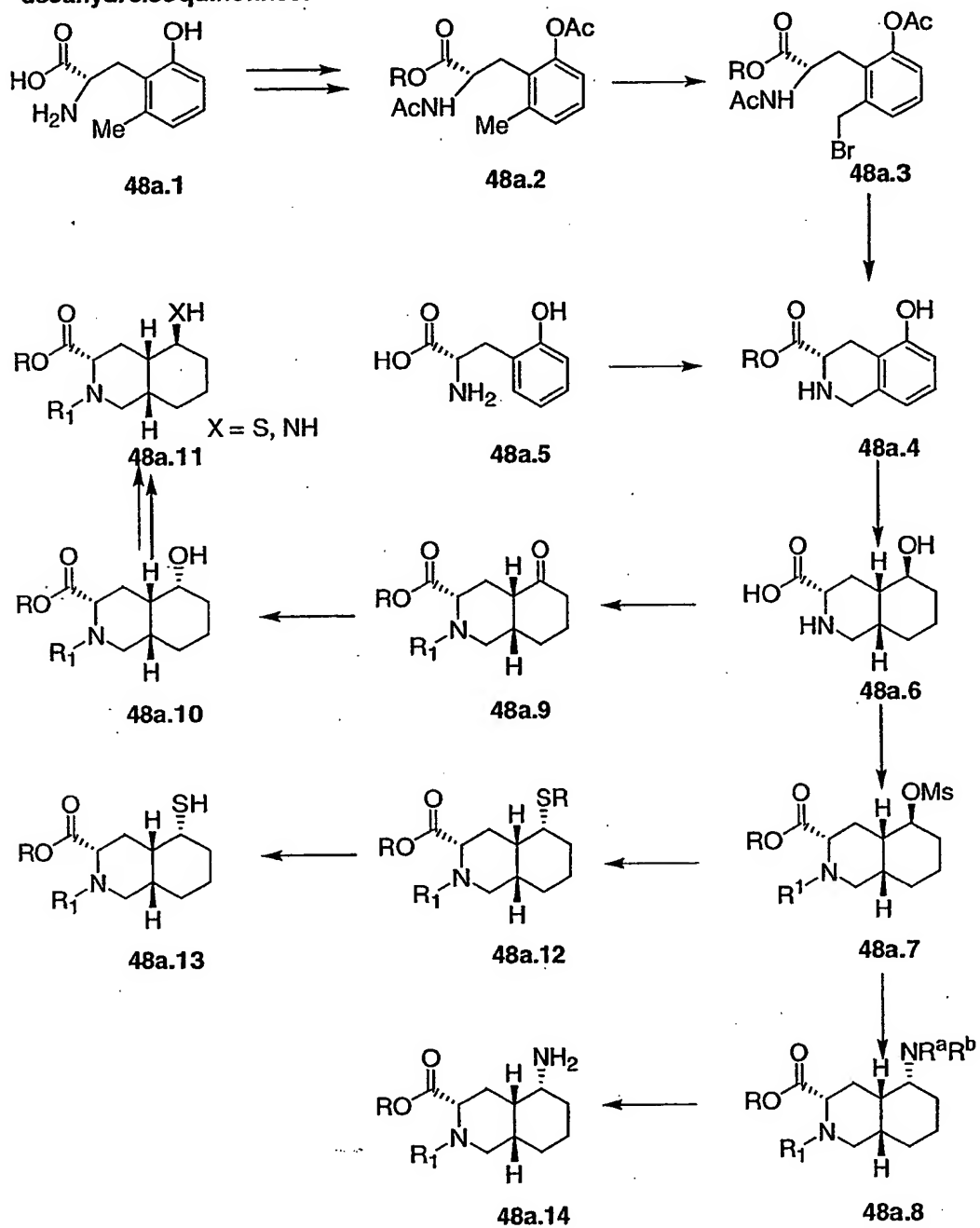
Scheme 53 illustrates the conversion of the latter group of compounds 53.1 (in which the group B is link-P(O)(OR¹)₂ or optionally protected precursor substituents thereto, such as, for example, OH, SH, NH₂) to the corresponding R⁴NH amides 53.5.

As shown in Scheme 53, the ester compounds 53.1 are deprotected to form the corresponding carboxylic acids 53.2. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R², and the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is removed by treatment with zinc in acetic acid, as described in J. Amer. Chem. Soc., 88, 852, 1966.

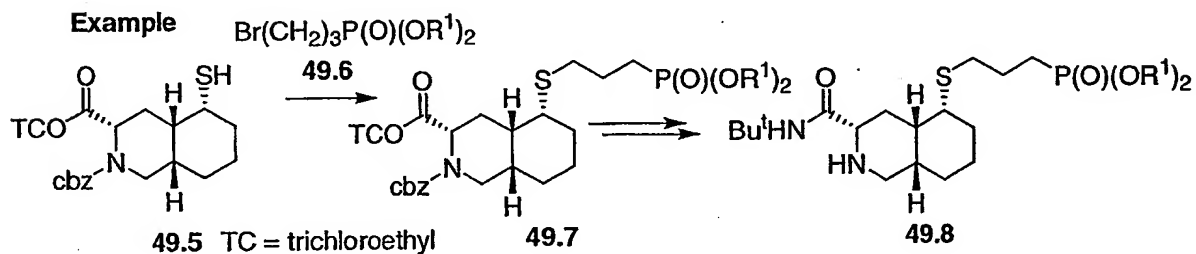
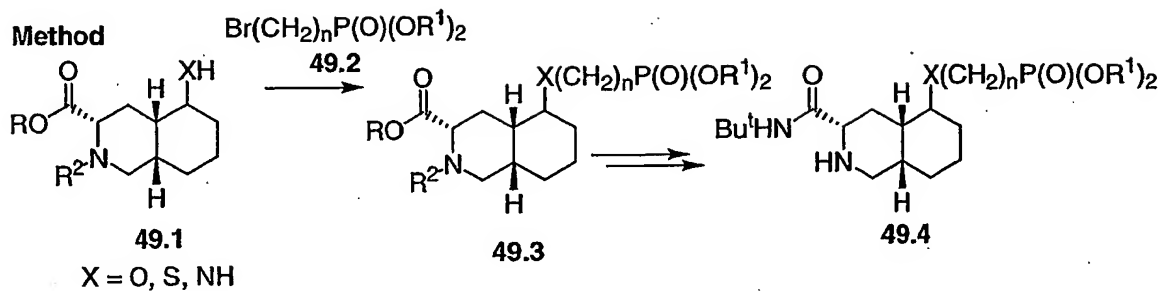
Conversion of the carboxylic acid 53.2 to the R^4NH amide 53.4 is then accomplished by reaction of the carboxylic acid, or an activated derivative thereof, with the amine R^4NH_2 53.3 to afford the amide 53.4, using the conditions described above for the preparation of the amide 1.6. Deprotection of the NR^2 group, as described above, then affords the free amine 53.5.

5

Scheme 48a. Intermediates for the preparation of phosphonate-containing decahydroisoquinolines.

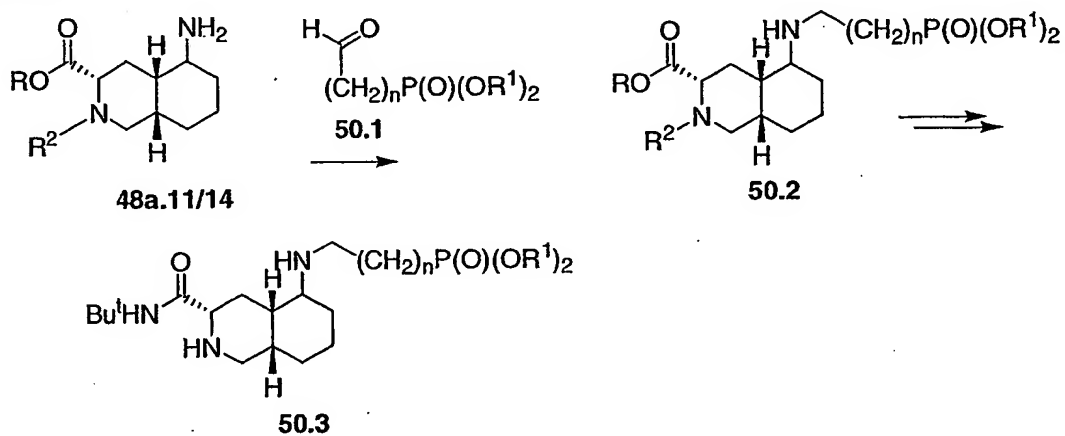


Scheme 49

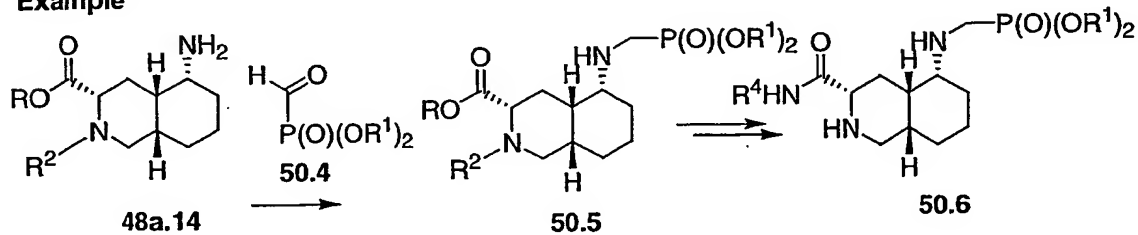


Scheme 50

Method

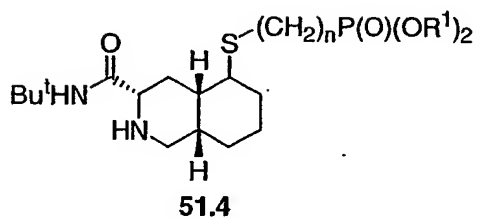
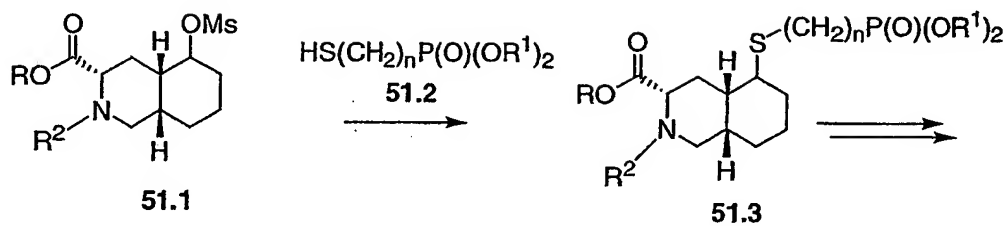


Example

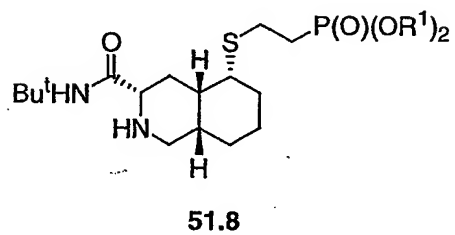
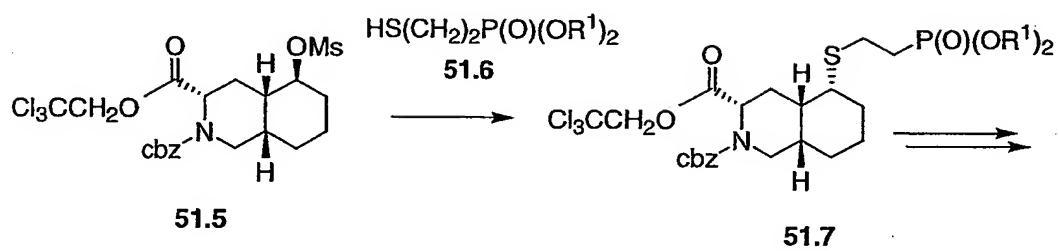


Scheme 51

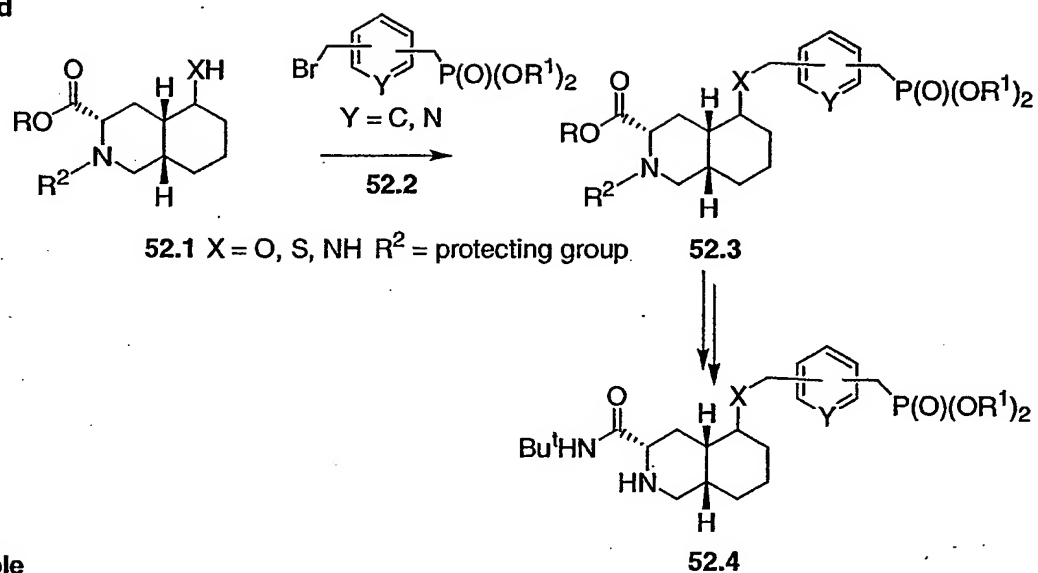
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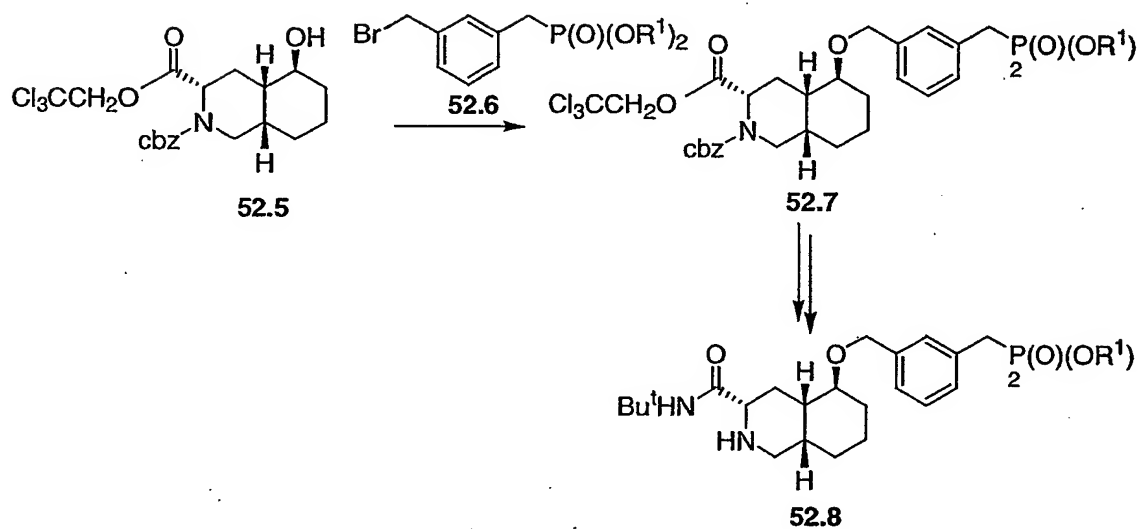
Example



Scheme 52
Method

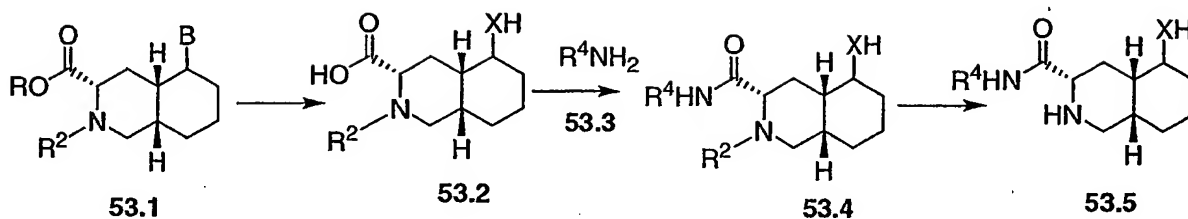


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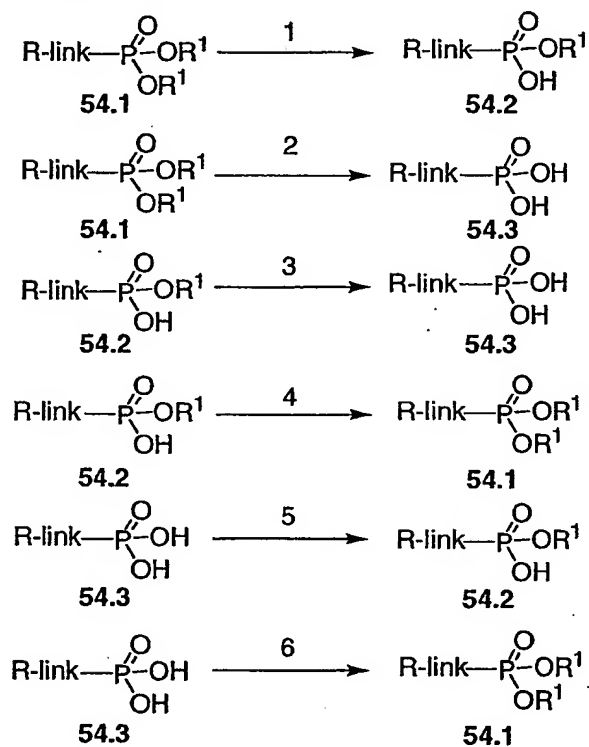


Scheme 53

Method



Scheme 54



Interconversions of the phosphonates $R\text{-link-P(O)(OR}^1\text{)}_2$, $R\text{-link-P(O)(OR}^1\text{)(OH)}$ and $R\text{-link-P(O)(OH)}_2$.

- 5 Schemes 1 - 69 described the preparations of phosphonate esters of the general structure $R\text{-link-P(O)(OR}^1\text{)}_2$, in which the groups R^1 , the structures of which are defined in Chart 1, may be the same or different. The R^1 groups attached to a phosphonate esters 1-6, or to precursors thereto, may be changed using established chemical transformations. The

interconversions reactions of phosphonates are illustrated in Scheme 54. The group R in Scheme 54 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1-6 or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-6. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 54.1 into the corresponding phosphonate monoester 54.2 (Scheme 54, Reaction 1) can be accomplished by a number of methods. For example, the ester 54.1 in which R¹ is an aralkyl group such as benzyl, can be converted into the monoester compound 54.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester 54.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 54.2 can be effected by treatment of the ester 54.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

Phosphonate diesters 54.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 54.2 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, can be converted into the monoester 54.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 54.1 or a phosphonate monoester 54.2 into the corresponding phosphonic acid 54.3 (Scheme 54, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 54.2 in which R¹ is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid

54.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester 54.2 in which R¹ is alkenyl such as, for example, allyl, can be converted into the phosphonic acid 54.3 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985.

Palladium catalyzed hydrogenolysis of phosphonate esters 54.1 in which R¹ is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters 54.1 in which R¹ is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.

The conversion of a phosphonate monoester 54.2 into a phosphonate diester 54.1 (Scheme 54, Reaction 4) in which the newly introduced R¹ group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate 54.2 is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yl)oxytripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester 54.2 to the diester 54.1 can be effected by the use of the Mitsunobu reaction, as described above (Scheme 25). The substrate is reacted with the hydroxy compound R¹OH, in the presence of diethyl azodicarboxylate and a triaryl phosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester 54.2 can be transformed into the phosphonate diester 54.1, in which the introduced R¹ group is alkenyl or aralkyl, by reaction of the monoester with the halide R¹Br, in which R¹ is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester 54.2 is transformed into the chloro analog RP(O)(OR¹)Cl by reaction with thionyl chloride or oxalyl chloride and the like, as described in *Organic Phosphorus Compounds*, G. M. Kosolapoff, L. Macir, eds, Wiley, 1976, p. 17, and the thus-obtained product RP(O)(OR¹)Cl is

then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester **54.1**.

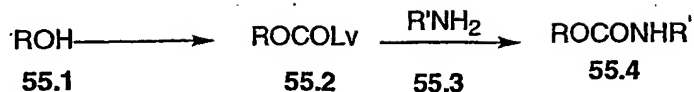
A phosphonic acid $R\text{-link-P(O)(OH)}_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme 54, Reaction 5) by means of the methods described above of for
5 the preparation of the phosphonate diester $R\text{-link-P(O)(OR}^1)_2$ **54.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid $R\text{-link-P(O)(OH)}_2$ **54.3** can be transformed into a phosphonate diester $R\text{-link-P(O)(OR}^1)_2$ **54.1** (Scheme 54, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and
10 triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine.

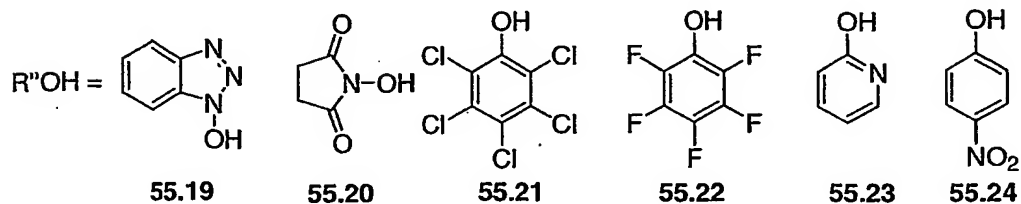
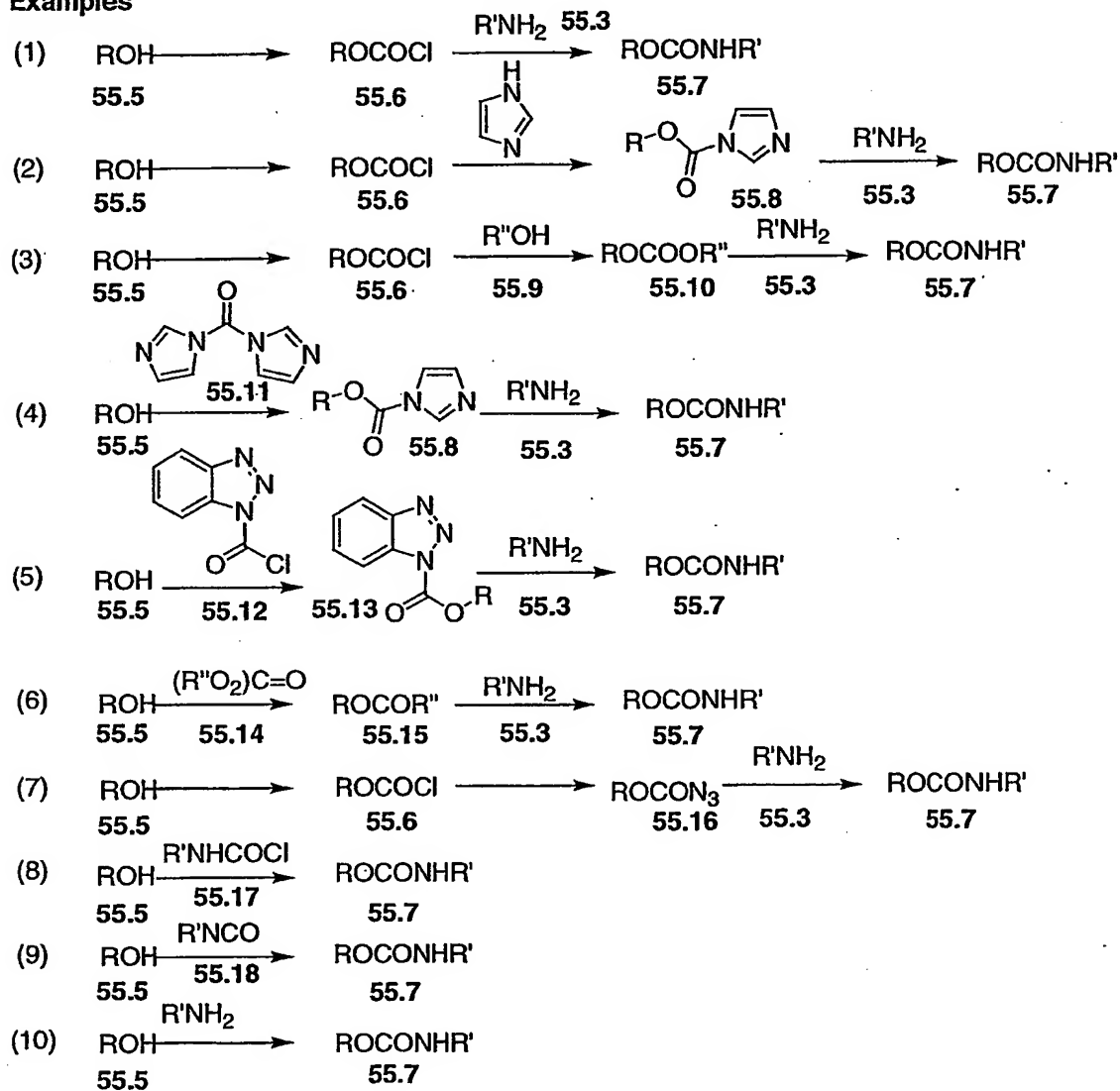
Alternatively, phosphonic acids **54.3** can be transformed into phosphonic esters **54.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°C. Alternatively, phosphonic acids **54.3** can be transformed into phosphonic esters **54.1** in which R^1 is alkenyl, by means of an alkylation reaction. The
15 phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **54.1**.

Scheme 55

General reaction



Examples



Preparation of the phosphonate esters 1-6 incorporating carbamate moieties.

The phosphonate esters 1-6 in which the R^6CO group is formally derived from the carboxylic acid synthons C39 - C49 as shown in Chart 2c, contain a carbamate moiety. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme 55 illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme 55, in the general reaction generating carbamates, a carbinol 55.1 is converted into the activated derivative 55.2 in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative 55.2 is then reacted with an amine 55.3, to afford the carbamate product 55.4. Examples 1 - 7 in Scheme 55 depict methods by which the general reaction can be effected. Examples 8 - 10 illustrate alternative methods for the preparation of carbamates.

Scheme 55, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol 55.5. In this procedure, the carbinol 55.5 is reacted with phosgene, in an inert solvent such as toluene, at about 0°C, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate 55.6. The latter compound is then reacted with the amine component 55.3, in the presence of an organic or inorganic base, to afford the carbamate 55.7. For example, the chloroformyl compound 55.6 is reacted with the amine 55.3 in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate 55.7. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 55, Example 2 depicts the reaction of the chloroformate compound 55.6 with imidazole, 55.7, to produce the imidazolide 55.8. The imidazolide product is then reacted with the amine 55.3 to yield the carbamate 55.7. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°C, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 55 Example 3, depicts the reaction of the chloroformate 55.6 with an activated hydroxyl compound $R''OH$, to yield the mixed carbonate ester 55.10. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component $R''OH$ is selected from the group of compounds 55.19 - 55.24 shown in Scheme 55, and similar compounds. For example, if the component $R''OH$ is hydroxybenztriazole 55.19, N-hydroxysuccinimide 55.20, or pentachlorophenol, 55.21, the mixed carbonate 55.10 is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component $R''OH$ is pentafluorophenol 55.22 or 2-hydroxypyridine 55.23 can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme 55 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 55.8 is employed. In this procedure, a carbinol 55.5 is reacted with an equimolar amount of carbonyl diimidazole 55.11 to prepare the intermediate 55.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 55.8 is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 55.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 55.7.

Scheme 55, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxy carbonylbenztriazole 55.13. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride 55.12, to afford the alkoxy carbonyl product 55.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine $R'NH_2$ to afford the carbamate 55.7. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80°C as described in Syn., 1977, 704.

Scheme 55, Example 6 illustrates the preparation of carbamates in which a carbonate $(R''O)_2CO$, 55.14, is reacted with a carbinol 55.5 to afford the intermediate alkyloxycarbonyl intermediate 55.15. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate 55.7. The procedure in which the reagent 55.15 is derived from

hydroxybenztriazole 55.19 is described in Synthesis, 1993, 908; the procedure in which the reagent 55.15 is derived from N-hydroxysuccinimide 55.20 is described in Tet. Lett., 1992, 2781; the procedure in which the reagent 55.15 is derived from 2-hydroxypyridine 55.23 is described in Tet. Lett., 1991, 4251; the procedure in which the reagent 55.15 is derived from 4-nitrophenol 55.24 is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate 55.14 is conducted in an inert organic solvent at ambient temperature.

Scheme 55, Example 7 illustrates the preparation of carbamates from alkoxycarbonyl azides 55.16. In this procedure, an alkyl chloroformate 55.6 is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide 55.16. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 55.7. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme 55, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate 55.7.

Scheme 55, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate 55.18. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate 55.7.

Scheme 55, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate 55.7.

Preparation of phosphonate intermediates 5 and 6 with phosphonate moieties incorporated into the group R^6COOH and $R^2NHCH(R^3)CONHR^4$.

The chemical transformations described in Schemes 1 - 55 illustrate the preparation of compounds 1-4 in which the phosphonate ester moiety is attached to the quinoline-2-carboxylate substructure, (Schemes 1-8), the phenylalanine or thiophenol moiety (Schemes 9-13), the tert-butylamine moiety (Schemes 14-18) and the decahydroisoquinoline moiety (Schemes 19 - 22).

The various chemical methods employed herein (Schemes 25 - 69) for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds $R^6\text{COOH}$, as defined in Charts 3a, 3b and 3c, and into the compounds $R^2\text{NHCH}(R^3)\text{CONHR}^4$ as defined in Chart 2. For example, Schemes 56 - 61 illustrate the preparation of phosphonate-containing analogs of the phenoxyacetic acid C8 (Chart 3a), Schemes 62 - 65 illustrate the preparation of phosphonate-containing analogs of the carboxylic acid C4, Schemes 66 - 69 illustrate the preparation of phosphonate-containing analogs of the amine A12 (Chart 2), and Schemes 70-75 illustrate the preparation of phosphonate-containing analogs of the carboxylic acid C38. The resultant phosphonate-containing analogs $R^{6a}\text{COOH}$ and $R^{2a}\text{NHCH}(R^{3a})\text{CONHR}^4$ can then, using the procedures described above, be employed in the preparation of the compounds 5 and 6. The procedures required for the introduction of the phosphonate-containing analogs $R^{6a}\text{COOH}$ and $R^{2a}\text{NHCH}(R^{3a})\text{CONHR}^4$ are the same as those described above for the introduction of the $R^6\text{CO}$ and $R^2\text{NHCH}(R^3)\text{CONHR}^4$ moieties.

Preparation of dimethylphenoxyacetic acids incorporating phosphonate moieties.

Scheme 56 illustrates two alternative methods by means of which 2,6-dimethylphenoxyacetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the 2,6-dimethylphenol moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed 2,6-dimethylphenoxyacetic acid intermediate. In the first sequence, a substituted 2,6-dimethylphenol 56.1, in which the substituent B is a precursor to the group $\text{link-P}(\text{O})(\text{OR}^1)_2$, and in which the phenolic hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound 56.2. Methods for

the conversion of the substituent B into the group $\text{link-P(O)(OR}^1\text{)}_2$ are described in Schemes 25 - 69.

The protected phenolic hydroxyl group present in the phosphonate-containing product 56.2 is then deprotected, using methods described below, to afford the phenol 56.3.

- 5 The phenolic product 56.3 is then transformed into the corresponding phenoxyacetic acid 56.4, in a two step procedure. In the first step, the phenol 56.3 is reacted with an ester of bromoacetic acid 56.5, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of
- 10 phenols to afford phenolic ethers is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the phenol and the alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.
- 15 Preferably, equimolar amounts of the phenol 56.3 and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described in U.S. Patent 5,914,332, to afford the ester 56.6.

- The thus-obtained ester 56.6 is then hydrolyzed to afford the carboxylic acid 56.4. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group
- 20 such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group, methods for hydrolysis are described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.
- 25 Preferably, the ester product 56.6 which R is ethyl is hydrolyzed to the carboxylic acid 56.4 by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in U.S. Patent 5,914,332.

- Alternatively, an appropriately substituted 2,6-dimethylphenol 56.7, in which the substituent B is a precursor to the group $\text{link-P(O)(OR}^1\text{)}_2$, is transformed into the corresponding phenoxyacetic ester 56.8. The conditions employed for the alkylation reaction are similar to
- 30 those described above for the conversion of the phenol 56.3 into the ester 56.6.

The phenolic ester 56.8 is then converted, by transformation of the group B into the group $\text{link-P(O)(OR}^1\text{)}_2$ followed by ester hydrolysis, into the carboxylic acid 56.4. The group B

which is present in the ester **56.4** may be transformed into the group link-P(O)(OR¹)₂ either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes **56** - **61** illustrate the preparation of 2,6-dimethylphenoxyacetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of phenoxyacetic esters **56.8**, with, if appropriate, modifications made according to the knowledge of one skilled in the art.

Scheme **57** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester which is attached to the phenolic group by means of a carbon chain incorporating a nitrogen atom. The compounds **57.4** are obtained by means of a reductive alkylation reaction between a 2,6-dimethylphenol aldehyde **57.1** and an aminoalkyl phosphonate ester **57.2**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component **57.2** and the aldehyde component **57.1** are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product **57.3**. The amination product **57.3** is then converted into the phenoxyacetic acid compound **57.4**, using the alkylation and ester hydrolysis procedures described above, (Scheme **56**)

For example, equimolar amounts of 4-hydroxy-3,5-dimethylbenzaldehyde **57.5** (Aldrich) and a dialkyl aminoethyl phosphonate **57.6**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in J. Amer. Chem. Soc., 91, 3996, 1969, to afford the amine product **57.3**. The product is then converted into the acetic acid **57.8**, as described above.

Using the above procedures, but employing, in place of the aldehyde **57.5**, different aldehydes **57.1**, and/or different aminoalkyl phosphonates **57.2**, the corresponding products **57.4** are obtained.

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described above (Scheme **54**)

Scheme 58 depicts the preparation of 2,6-dimethylphenols incorporating a phosphonate group linked to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected bromo-substituted 2,6-dimethylphenol 58.1 is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate 58.2. The coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product 58.3 is converted, using the procedures described above, (Scheme 56) into the corresponding phenoxyacetic acid 58.4. Alternatively, the olefinic product 58.3 is reduced to afford the saturated 2,6-dimethylphenol derivative 58.5. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or diimide. Following the reduction reaction, the product 58.5 is converted, as described above, (Scheme 56) into the corresponding phenoxyacetic acid 58.6. For example, 3-bromo-2,6-dimethylphenol 58.7, prepared as described in Can. J. Chem., 1983, 61, 1045, is converted into the tert-butyldimethylsilyl ether 58.8, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product 58.8 is reacted with an equimolar amount of a dialkyl allyl phosphonate 58.9, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°C, to produce the coupled product 58.10. The silyl group is removed, for example by the treatment of the ether 58.10 with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol 58.11. This compound is converted, employing the procedures described above, (Scheme 56) into the corresponding phenoxyacetic acid 58.12. Alternatively, the unsaturated compound 58.11 is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog 58.13. This compound is

converted, employing the procedures described above, (Scheme 56) into the corresponding phenoxyacetic acid 58.14.

Using the above procedures, but employing, in place of 3-bromo-2,6-dimethylphenol 58.7, different bromophenols 58.1, and/or different dialkyl alkenyl phosphonates 58.2, the
5 corresponding products 58.4 and 58.6 are obtained.

Scheme 59 illustrates the preparation of phosphonate-containing 2,6-dimethylphenoxyacetic acids 59.1 in which the phosphonate group is attached to the 2,6-dimethylphenoxy moiety by means of a carbocyclic ring. In this procedure, a bromo-substituted 2,6-dimethylphenol 59.2
10 is converted, using the procedures illustrated in Scheme 56, into the corresponding 2,6-dimethylphenoxyacetic ester 59.3. The latter compound is then reacted, by means of a palladium-catalyzed Heck reaction, with a cycloalkenone 59.4, in which n is 1 or 2. The coupling reaction is conducted under the same conditions as those described above for the preparation of 58.3 (Scheme 58). The product 59.5 is then reduced catalytically, as described
15 above for the reduction of 58.3, (Scheme 58), to afford the substituted cycloalkanone 59.6. The ketone is then subjected to a reductive amination procedure, by reaction with a dialkyl 2-aminoethylphosphonate 59.7 and sodium triacetoxyborohydride, as described in J. Org. Chem., 61, 3849, 1996, to yield the amine phosphonate 59.8. The reductive amination reaction is conducted under the same conditions as those described above for the preparation
20 of the amine 57.3 (Scheme 57). The resultant ester 59.8 is then hydrolyzed, as described above, to afford the phenoxyacetic acid 59.1.

For example, 4-bromo-2,6-dimethylphenol 59.9 (Aldrich) is converted, as described above, into the phenoxy ester 59.10. The latter compound is then coupled, in dimethylformamide solution at ca. 60°C, with cyclohexenone 59.11, in the presence of
25 tetrakis(triphenylphosphine)palladium(0) and triethylamine, to yield the cyclohexenone 59.12. The enone is then reduced to the saturated ketone 59.13, by means of catalytic hydrogenation employing 5% palladium on carbon as catalyst. The saturated ketone is then reacted with an equimolar amount of a dialkyl aminoethylphosphonate 59.14, prepared as described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the amine 59.15.
30 Hydrolysis, employing lithium hydroxide in aqueous methanol at ambient temperature, then yields the acetic acid 59.16.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylphenol **59.9**, different bromo-substituted 2,6-dimethylphenols **59.2**, and/or different cycloalkenones **59.4**, and/or different dialkyl aminoalkylphosphonates **59.7**, the corresponding products **59.1** are obtained.

5

Scheme **60** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate group attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an optionally protected hydroxy, thio or amino-substituted 2,6-dimethylphenol **60.1** is reacted, in the presence of a base such as, for example, potassium carbonate, and optionally in the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate **60.2**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°C. The product of the alkylation reaction, **60.3** is then converted, as described above (Scheme **56**) into the phenoxyacetic acid **60.4**.

10

For example, 2,6-dimethyl-4-mercaptophenol **60.5**, prepared as described in EP 482342, is reacted in dimethylformamide at ca. 60°C with an equimolar amount of a dialkyl bromobutyl phosphonate **60.6**, the preparation of which is described in Synthesis, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the thioether product **60.7**. This compound is converted, employing the procedures described above, (Scheme **56**) into the corresponding phenoxyacetic acid **60.8**.

15

Using the above procedures, but employing, in place of 2,6-dimethyl-4-mercaptophenol **60.5**, different hydroxy, thio or aminophenols **60.1**, and/or different dialkyl bromoalkyl phosphonates **60.2**, the corresponding products **60.4** are obtained.

20

Scheme **61** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester group attached by means of an aromatic or heteroaromatic group. In this procedure, an optionally protected hydroxy, mercapto or amino-substituted 2,6-dimethylphenol **61.1** is reacted, under basic conditions, with a bis(halomethyl)aryl or heteroaryl compound **61.2**. Equimolar amounts of the phenol and the halomethyl compound are reacted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium or cesium carbonate, or dimethylaminopyridine, to afford

25

30

the ether, thioether or amino product **61.3**. The product **61.3** is then converted, using the procedures described above, (Scheme 56) into the phenoxyacetic ester **61.4**. The latter compound is then subjected to an Arbuzov reaction by reaction with a trialkylphosphite **61.5** at ca. 100°C to afford the phosphonate ester **61.6**. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992, 115. The resultant product **61.6** is then converted into the acetic acid **61.7** by hydrolysis of the ester moiety, using the procedures described above, (Scheme 56).

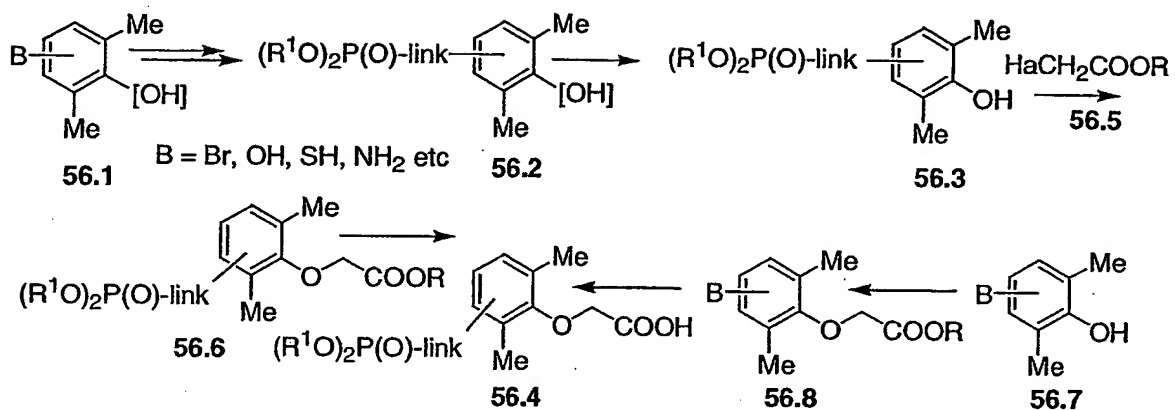
For example, 4-hydroxy-2,6-dimethylphenol **61.8** (Aldrich) is reacted with one molar equivalent of 3,5-bis(chloromethyl)pyridine, the preparation of which is described in Eur. J.

Inorg. Chem., 1998, 2, 163, to afford the ether **61.10**. The reaction is conducted in acetonitrile at ambient temperature in the presence of five molar equivalents of potassium carbonate. The product **61.10** is then reacted with ethyl bromoacetate, using the procedures described above, (Scheme 56) to afford the phenoxyacetic ester **61.11**. This product is heated at 100°C for 3 hours with three molar equivalents of triethyl phosphite **61.12**, to afford the phosphonate ester **61.13**. Hydrolysis of the acetic ester moiety, as described above, for example by reaction with lithium hydroxide in aqueous ethanol, then affords the phenoxyacetic acid **61.14**.

Using the above procedures, but employing, in place of the bis(chloromethyl) pyridine **61.9**, different bis(halomethyl) aromatic or heteroaromatic compounds **61.2**, and/or different

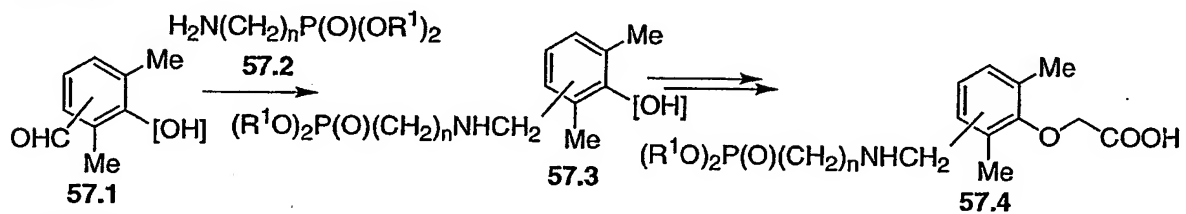
hydroxy, mercapto or amino-substituted 2,6-dimethylphenols **61.1** and/or different trialkyl phosphites **61.5**, the corresponding products **61.7** are obtained.

Scheme 56

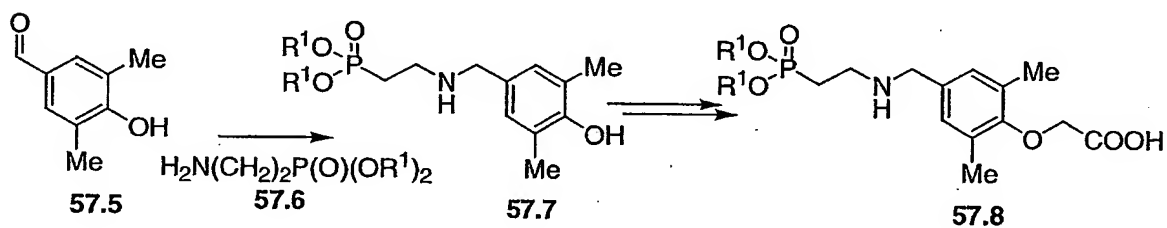


Scheme 57

Method

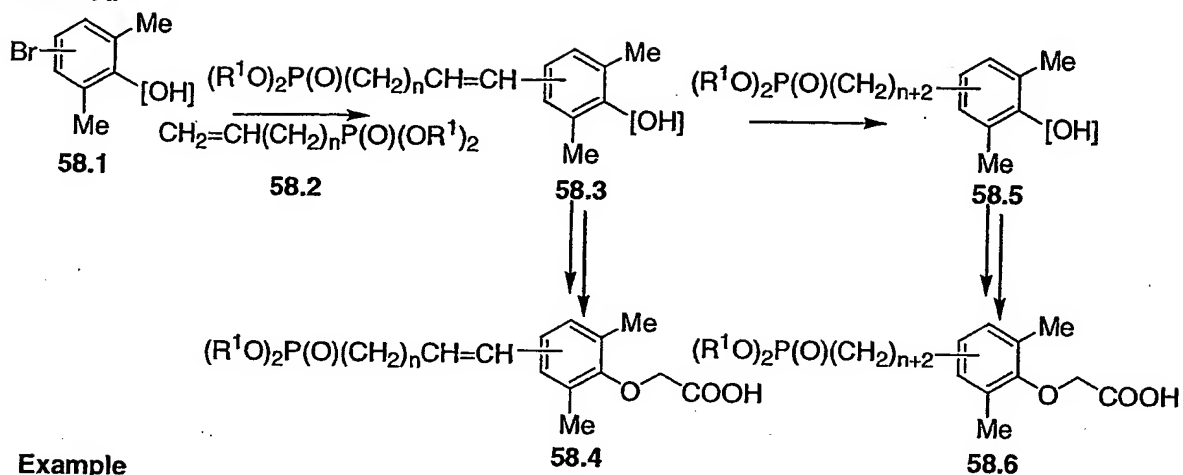


Example

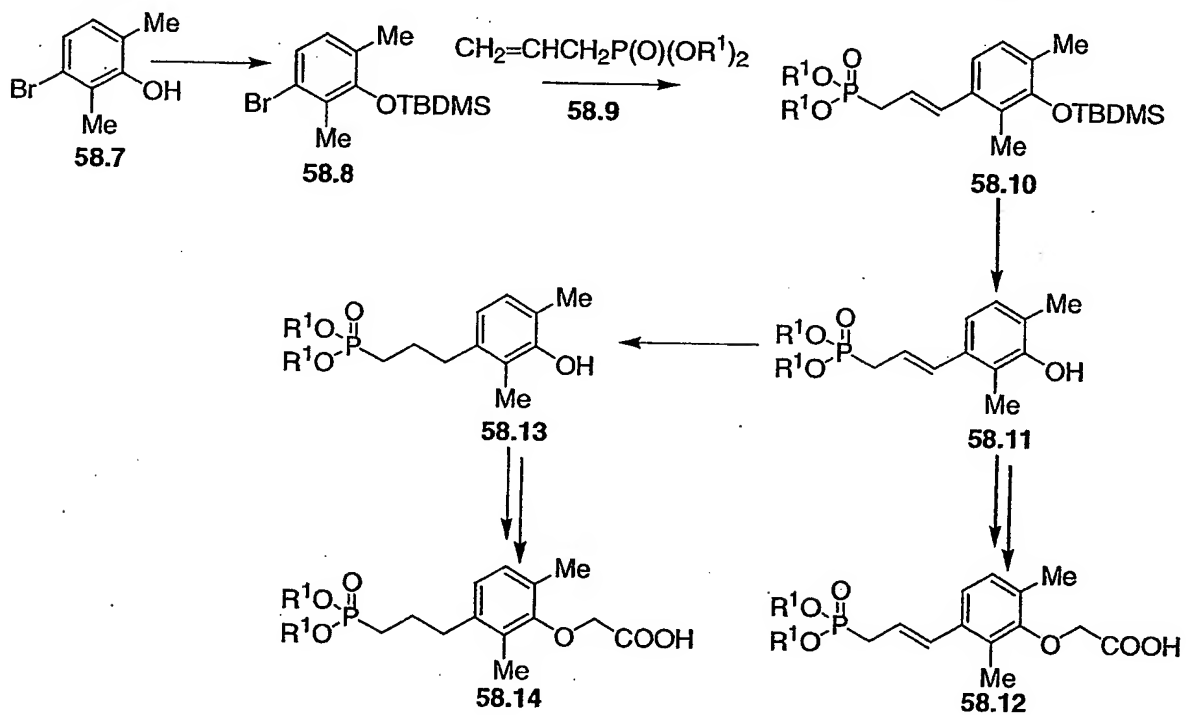


Scheme 58

Method

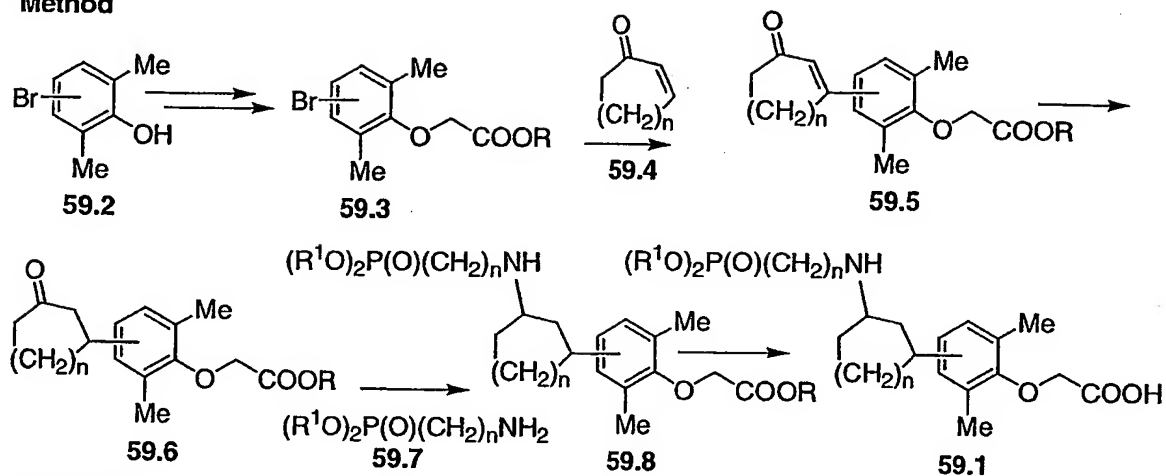


Example

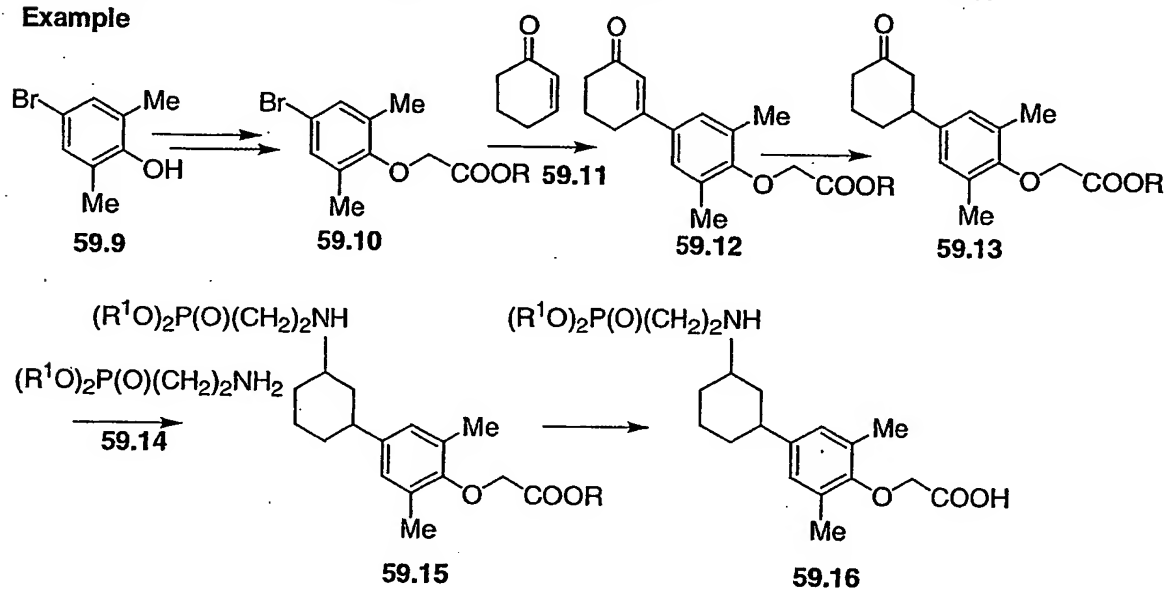


Scheme 59

Method

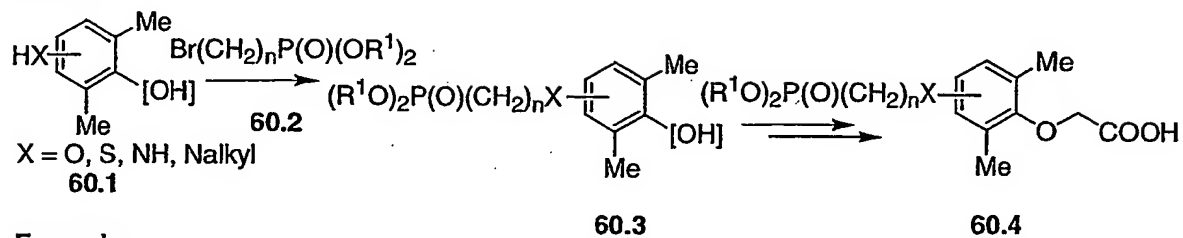


Example

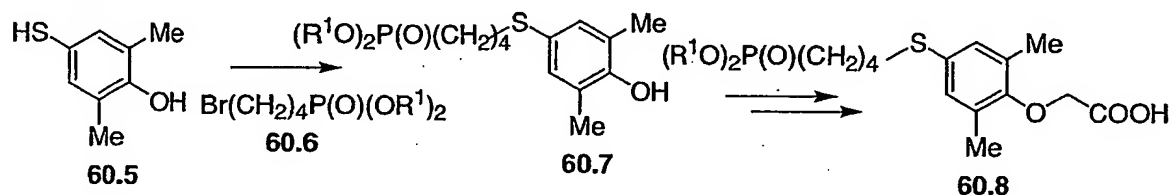


Scheme 60

Method

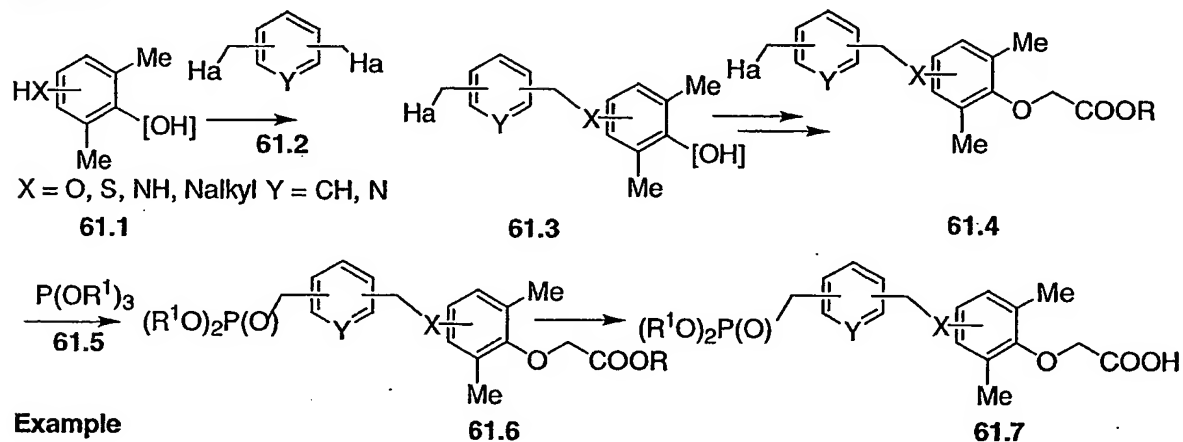


Example

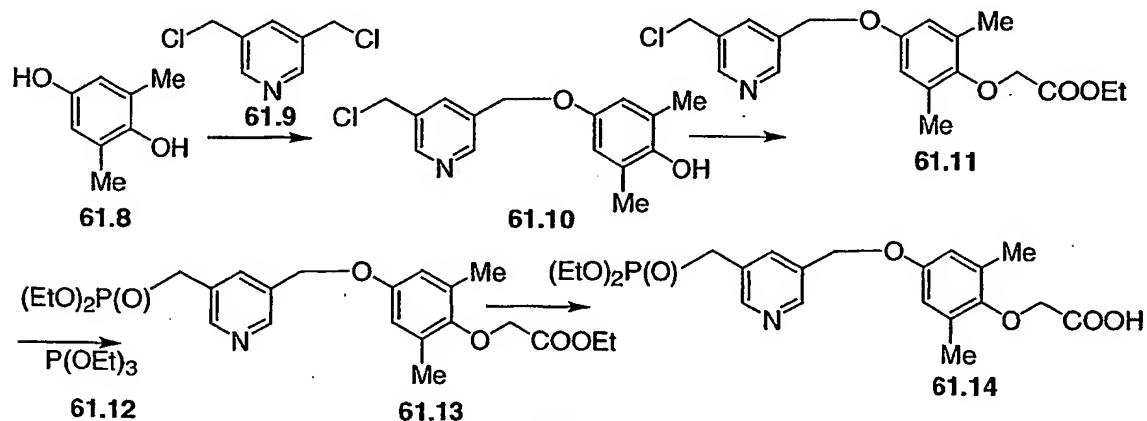


Scheme 61

Method



Example



Preparation of benzyl carbamate compounds incorporating phosphonate groups.

5 Scheme 62 depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative C4 in which the phosphonate moiety is either directly attached to the phenyl ring or attached by means of an alkylene chain. In this procedure, a dialkyl hydroxymethylphenyl alkylphosphonate 62.1 is converted into an activated derivative 62.2, in which Lv is a leaving group, as described above (Scheme 55). The product is then reacted
10 with a suitably protected aminoacid 62.3, to afford the carbamate product 62.4. The reaction is conducted under the conditions described above for the preparation of carbamates (Scheme 55). The protecting group on the carboxylic acid group in the product 62.4 is then removed to afford the free carboxylic acid 62.5. Methods for the protection and deprotection of carboxylic acids are described, for example, in Protective Groups in Organic Synthesis, by
15 T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

For example, as shown in Scheme 62, Example 1, a dialkyl 4-hydroxymethylphenyl phosphonate 62.6, prepared as described in US 5569664, is reacted with phosgene, or an equivalent thereof, as described above (Scheme 55), to afford the chloroformyl product 62.7. This compound is then reacted in an inert solvent such as dichloromethane or tetrahydrofuran,
20 with the tert. butyl aminoacid ester 62.3, in the presence of a base such as triethylamine, to yield the carbamate product 62.8. The conversion of acids into tert. butyl esters is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 245ff. The ester can be prepared by the reaction of the carboxylic acid with isobutylene and an acid catalyst, or by conventional esterification procedures employing tert.
25 butanol. The tert. butyl protecting group is then removed from the product 62.8, for example by reaction with trifluoroacetic acid at ambient temperature for about one hour, to afford the carboxylic acid 62.9.

As a further example, Scheme 62, Example 2 shows the conversion of a dialkyl 4-hydroxymethyl benzyl phosphonate 62.10, prepared as described in J. Am. Chem. Soc., 1996,
30 118, 5881, into the hydroxybenztriazole derivative 62.11. The reaction is performed as described above (Scheme 55). The activated derivative is then reacted with the aminoacid

derivative 62.3, as described above, to afford the carbamate 62.12. deprotection, as previously described, then affords the carboxylic acid 62.13.

Using the above procedures, but employing, in place of the phosphonates 62.6 and 62.10, different phosphonates 62.1, and/or different aminoacid derivatives 62.3, the corresponding products 62.5 are obtained.

Scheme 63 depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative C4 in which the phosphonate moiety is attached to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted benzyl alcohol 63.1 is subjected to a palladium catalyzed Heck reaction, as described above, (Scheme 26) with a dialkyl alkenyl phosphonate 63.2, to afford the olefinic product 63.3. The product is then converted into the activated derivative 63.4, which is then reacted with aminoacid derivative 62.3, as described above, to afford, after deprotection of the carboxyl group, the carbamate product 63.5. Optionally, the olefinic coupling product can be reduced to the saturated analog 63.6. The reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5. The product 63.6 is then converted, as described above, into the carbamate derivative 63.8.

For example, 3-bromobenzyl alcohol 63.9 is coupled in acetonitrile solution, with a dialkyl allylphosphonate 63.10 (Aldrich), in the presence of palladium acetate, triethylamine and tri-*o*-tolylphosphine, as described in Synthesis, 1983, 556, to afford the product 63.11. This material is then reacted with carbonyl diimidazole, as described above, (Scheme 55) to afford the imidazolide 63.12. The product is then coupled with the aminoacid derivative 62.3, to afford after deprotection, the product 63.13. Alternatively, the unsaturated phosphonate 63.11 is reduced, for example by reaction with diborane in tetrahydrofuran at ambient temperature, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5., to afford the saturated analog 63.14. The latter compound is then transformed, as described above, into the carbamate aminoacid derivative 63.15.

Using the above procedures, but employing, in place of the 3-bromobenzyl alcohol 63.9, different bromobenzyl alcohols 63.1, and/or different alkenyl phosphonates 63.2, and/or different amino acid derivatives, the corresponding products 63.5 and 63.8 are obtained.

Scheme 64 depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative C4 in which the phosphonate moiety is attached to the phenyl ring by means of an amino-containing alkylene chain. In this procedure, a formyl-substituted benzyl alcohol 64.1 is converted, using the procedures described above in Schemes 55 and 63, into the aminoacid carbamate derivative 64.2. The product is then subjected to a reductive amination reaction with a dialkyl aminoalkyl phosphonate 64.3, to afford the phosphonate product 64.4. Reductive amination of carbonyl compounds is described above (Scheme 27). For example, 3-formyl benzyl alcohol 64.5 is converted into the carbamate derivative 64.6. The product is then reacted in ethanol solution at ambient temperature with a dialkyl aminoethyl phosphonate 64.7, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the phosphonate product 64.8. Using the above procedures, but employing, in place of the 3-formylbenzyl alcohol 64.5, different formylbenzyl alcohols 64.1, and/or different aminoalkyl phosphonates 64.3, the corresponding products 64.4 are obtained.

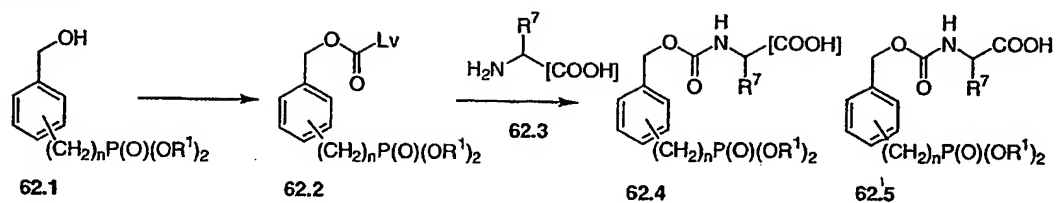
Scheme 65 depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative C4 in which the phosphonate moiety is attached to the phenyl ring by means of an O, S or N-alkyl-containing alkylene chain. In this procedure, a chloromethyl-substituted benzyl alcohol 65.1 is reacted with a dialkyl hydroxy, mercapto or alkylaminoalkyl phosphonate 65.2. The alkylation reaction is conducted between equimolar amounts of the reactants in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of an inorganic or organic base, such as diisopropylethylamine, dimethylaminopyridine, potassium carbonate and the like. The alkylated product 65.3 is then converted, as previously described, into the carbamate aminoacid derivative 65.4.

For example, 4-chloromethylbenzyl alcohol 65.5, (Aldrich) is reacted at ca. 60°C in acetonitrile solution with a dialkyl hydroxypropyl phosphonate 65.6, the preparation of which is described in Zh. Obshchei. Khim., 1974, 44, 1834, in the presence of dimethylaminopyridine, to afford the ether product 65.7. The product is then converted, as previously described, into the carbamate derivative 65.8.

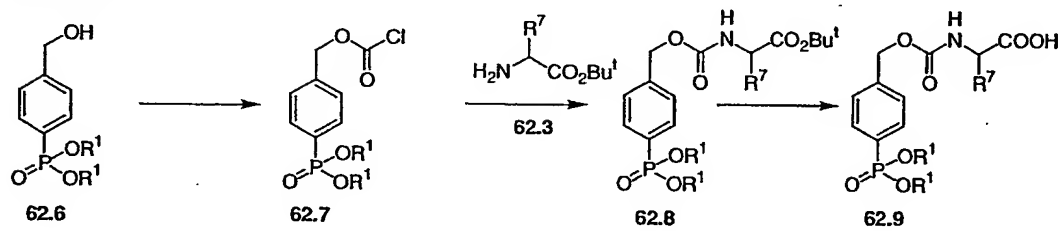
Using the above procedures, but employing, in place of 4-(chloromethyl)benzyl alcohol 65.5, different chloromethyl benzyl alcohols 65.1, and/or different hydroxy, mercapto or alkylamino phosphonates 65.2, the corresponding products 65.4 are obtained.

Scheme 62

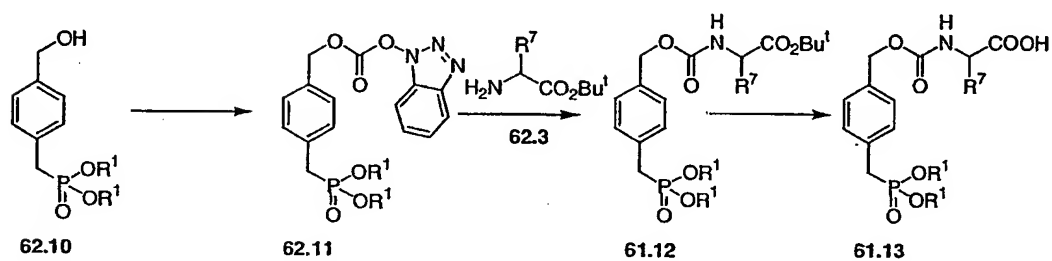
Method



Example 1

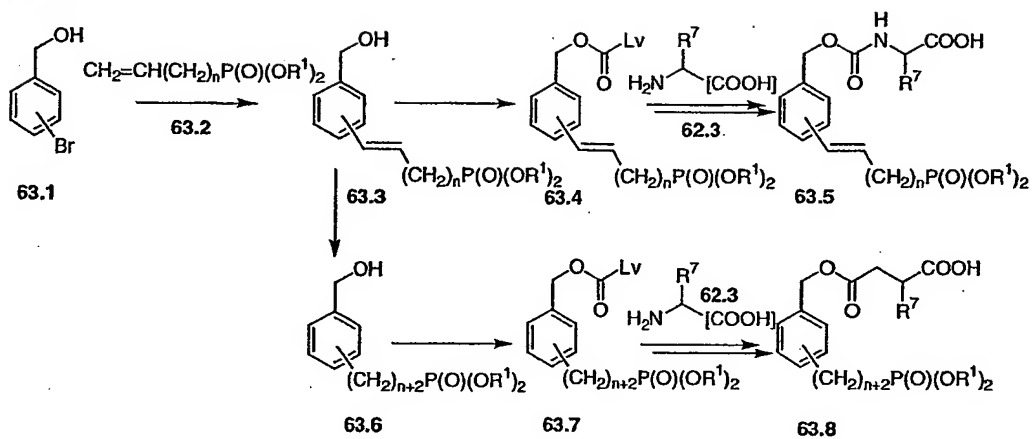


Example 2

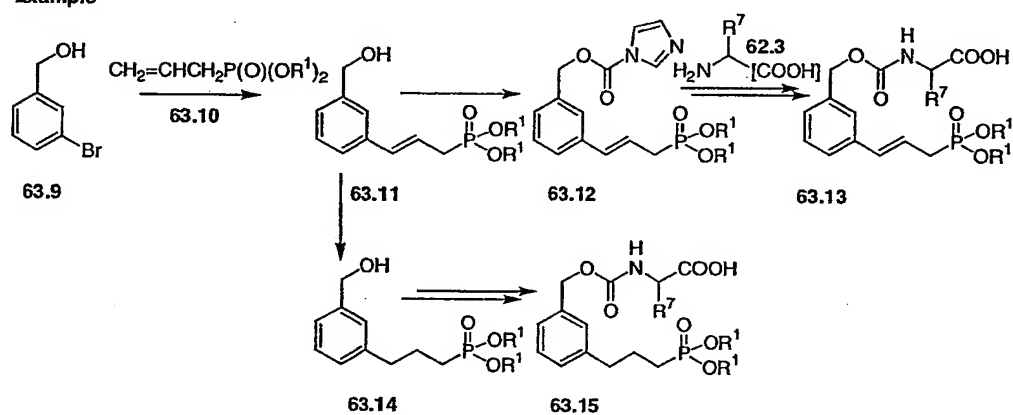


Scheme 63

Method

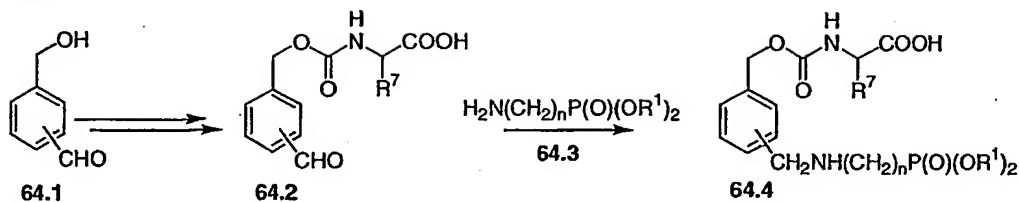


Example

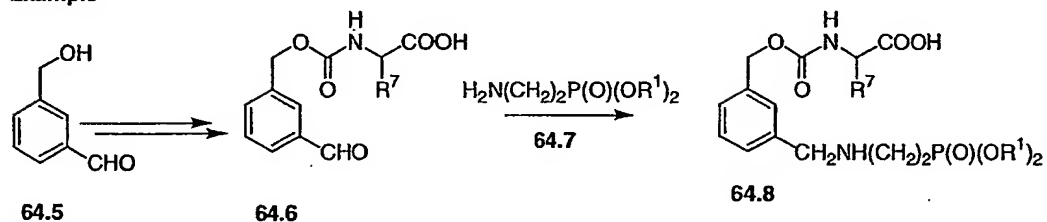


Scheme 64

Method

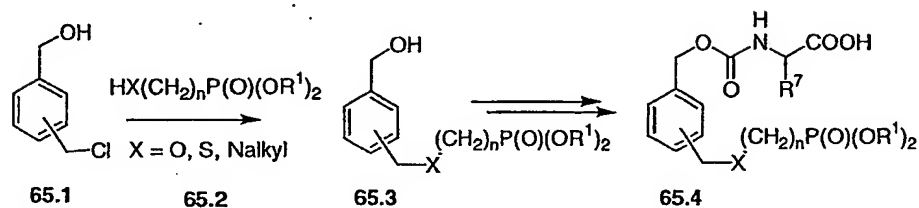


Example

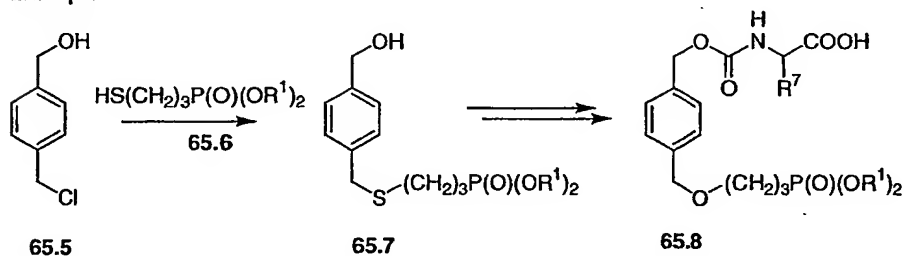


Scheme 65

Method



Example



Preparation of pyridinyloxymethyl piperidine derivatives incorporating phosphonate groups.

5

Scheme 66 illustrates the preparation of phosphonate-containing analogs of the amine A12 in which the phosphonate moiety is attached to the pyridine ring by means of a heteroatom and an alkylene chain. In this procedure, 2-bromo-4-hydroxymethylpyridine, the preparation of which is described in Chem. Pharm. Bull., 1990, 38, 2446, is subjected to a nucleophilic

- displacement reaction with a dialkyl hydroxy, thio or aminoalkyl-substituted alkyl phosphonate
- 66.2. The preparation of pyridine ethers, thioethers and amines by means of displacement reactions of 2-bromopyridines by alcohols, thiols and amines is described, for example, in Heterocyclic Compounds, Volume 3, R. A. Abramovitch, ed., Wiley, 1975, p. 597, 191, and
- 5 41 respectively. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide at ca 100°C in the presence of a base such as potassium carbonate. The displacement product 66.3 is then converted into the activated derivative 66.4, in which Lv is a leaving group such as halo, methanesulfonyloxy, p-toluenesulfonyloxy and the like. The conversion of alcohols into chlorides and bromides is described, for example, in
- 10 Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. For example, benzyl alcohols can be transformed into the chloro compounds, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols can be transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc.,
- 15 92, 2139, 1970. Alcohols can be converted into sulfonate esters by treatment with the alkyl or aryl sulfonyl chloride and a base, in a solvent such as dichloromethane or pyridine. Preferably, the carbinol 66.3 is converted into the corresponding chloro compound, 66.4, in which Lv is Cl, as described above. The product is then reacted with the piperidinol derivative 66.5. The preparation of the compounds 66.5 is described in U.S. 5,614,533, and in J. Org. Chem.,
- 20 1997, 62, 3440. The piperidinol derivative 66.5 is treated in dimethylformamide with a strong base such as sodium hydride, and the alkylating agent 66.4 is then added. The reaction proceeds to afford the ether product 66.6, and the BOC protecting group is then removed to yield the free amine compound 66.7. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley,
- 25 Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC group is removed by treatment of the substrate 66.6 with hydrochloric acid, as described in J. Org. Chem., 1997, 62, 3440.
- 30 For example, 2-bromo-4-hydroxymethylpyridine 66.1 the preparation of which is described in Chem. Pharm. Bull., 1990, 38, 2446, is reacted in dimethylformamide solution at ca 80°C with an equimolar amount of a dialkyl mercaptoethyl phosphonate 66.8, prepared as described in

Zh. Obschei. Khim., 1973, 43, 2364, and potassium carbonate, to yield the thioether product 66.9. The product is then reacted with one molar equivalent of methanesulfonyl chloride in pyridine at 0°C, to produce the mesylate compound 66.10. This material is reacted with the piperidinol reagent 66.5, using the conditions described above, to afford the ether 66.11. The BOC protecting group is then removed as previously described, to afford the amine product 66.12.

Using the above procedures, but employing, in place of the mercaptoethyl phosphonate 66.8, different hydroxy, mercapto or alkylamino phosphonates 66.2, the corresponding products 66.7 are obtained.

10

Scheme 67 illustrates the preparation of phosphonate-containing analogs of the amine A12 in which the phosphonate moiety is directly attached to the pyridine ring. In this procedure, a bromo-substituted 4-hydroxymethylpyridine 67.1 is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 67.2. The reaction between aryl bromides and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, 56, 1981, and in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°C, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The thus-obtained pyridylphosphonate 67.3 is then converted, as described above (Scheme 66) into an activated derivative 67.4, and the latter compound is transformed as described above into the amine 67.5.

20

For example, 3-bromo-4-hydroxymethylpyridine 67.5, prepared as described in Bioorg. Med. Chem. Lett., 1992, 2, 1619, is reacted with a dialkyl phosphite 67.2, as described above, to prepare the phosphonate 67.7. The product is then transformed into the chloro derivative by reaction with triphenylphosphine and N-chlorosuccinimide, and the product is converted, as described above (Scheme 66) into the amine 67.9.

25

Using the above procedures, but employing, in place of the 3-bromopyridine derivative 67.6, different bromopyridines 67.1, and/or different phosphites, the corresponding products 67.5 are obtained.

30

Scheme 68 illustrates the preparation of phosphonate-containing analogs of the amine A12 in which the phosphonate moiety is attached to the pyridine ring by means of an amine group and

an alkyl chain. In this procedure, an amino-substituted 4-hydroxymethylpyridine **68.1** is subjected to a reductive amination reaction with a dialkyl formylalkyl phosphonate **68.2**. The preparation of amines by means of reductive amination procedures is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, p. 421, and in *Advanced Organic Chemistry, Part B*, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990. The amine product **68.3** is then converted, as described above, into the piperidine derivative **68.5**. For example, 2-amino-4-hydroxymethylpyridine **68.6**, prepared as described in *Aust. J. Chem.*, 1993, 46, 9897, is reacted in ethanol solution with a dialkyl formylmethylphosphonate **68.7**, prepared as described in *Zh. Obschei. Khim.*, 1987, 57, 2793, in the presence of sodium cyanoborohydride, to yield the amine product **68.8**. This material is then transformed into the chloro derivative **68.9** by reaction with hydrogen chloride in ether. The chloro product is then transformed, as described above, into the piperidine derivative **68.10**. Using the above procedures, but employing, in place of the 2-aminopyridine derivative **68.6**, different aminopyridines **68.1**, and/or different formylalkyl phosphonates **68.2** the corresponding products **68.5** are obtained.

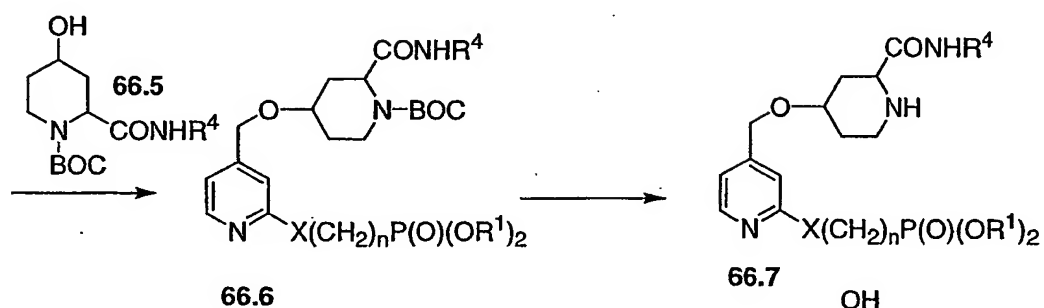
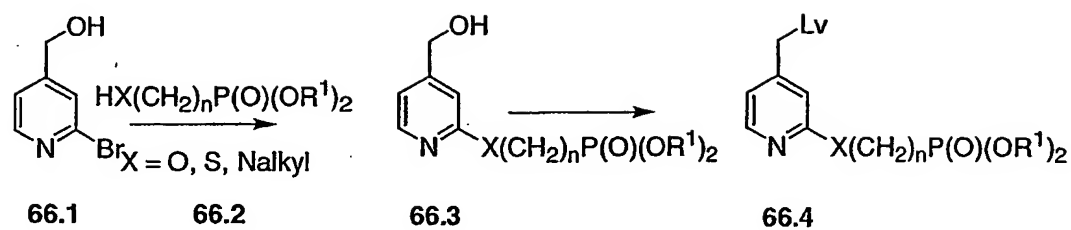
Scheme 69 illustrates the preparation of phosphonate-containing analogs of the amine **A12** in which the phosphonate moiety is attached to the pyridine ring by means of a saturated or unsaturated alkyl chain. In this procedure, a bromo-substituted 4-hydroxymethylpyridine **69.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **69.2**. The coupling of aryl bromides and olefins is described above (Scheme 26). The product is then converted, as described above, into the piperidine derivative **69.5**. Optionally, the latter compound can be reduced, for example as described above in Scheme 26, to afford the saturated analog **69.6**. For example, 3-bromo-4-hydroxymethylpyridine **69.7**, prepared as described in *Bioorg. Med. Chem. Lett.*, 1992, 2, 1619, is coupled with a dialkyl vinylphosphonate **69.8**, prepared as described in *Synthesis*, 1983, 556, to yield the olefinic product **69.9**. The product is reacted

with one molar equivalent of p-toluenesulfonyl chloride in pyridine at ambient temperature to afford the tosylate **69.10**. The latter compound is then transformed, as previously described, into the piperidine derivative **69.11**. Optionally, the latter compound is reduced, for example by reaction with diimide, to yield the saturated analog **69.12**.

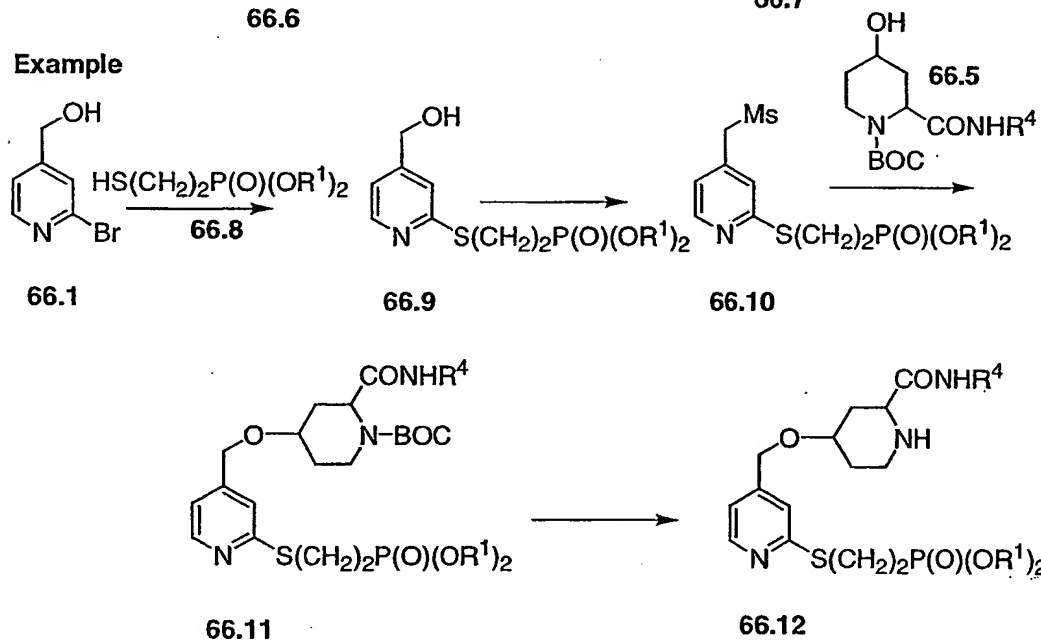
- 5 Using the above procedures, but employing, in place of the 3-bromopyridine derivative **69.7**, different bromopyridines **69.1**, and/or different alkenyl phosphonates **69.2** the corresponding products **69.5** and **69.6** are obtained.

Scheme 66

Method

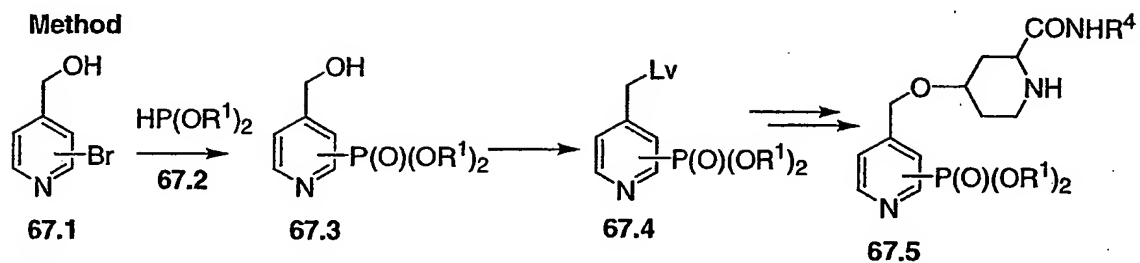


Example

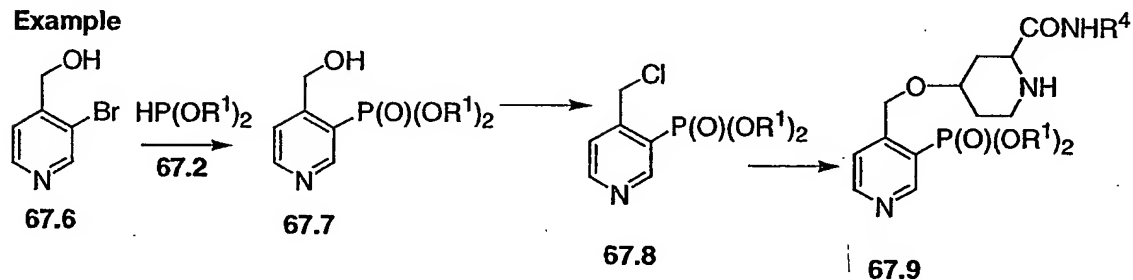


Scheme 67

Method

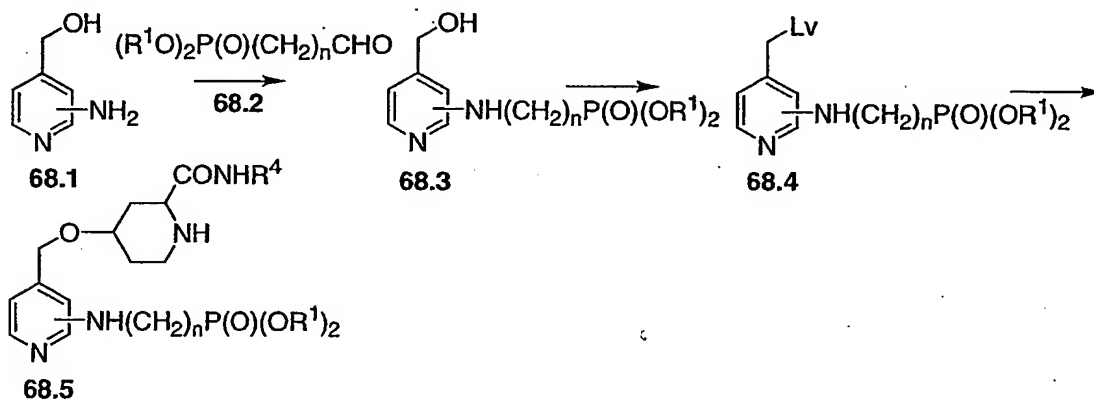


Example

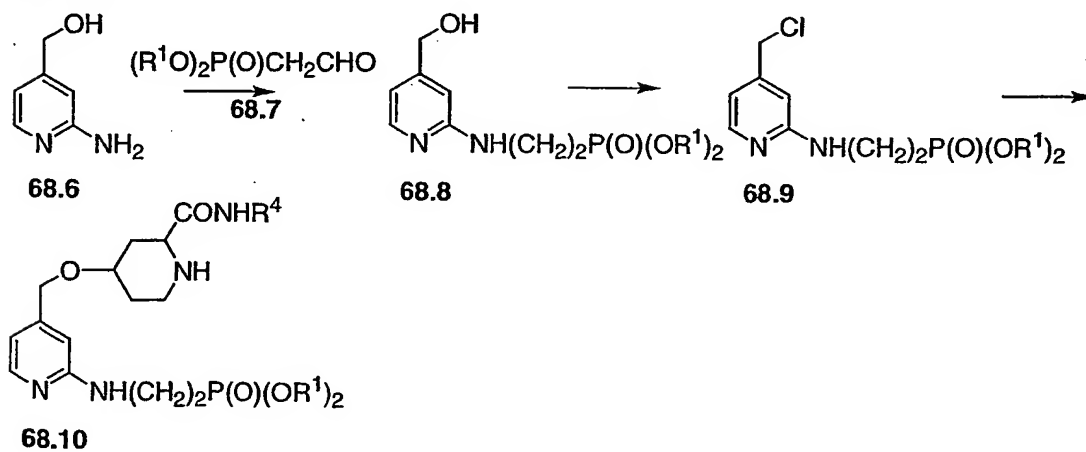


Scheme 68

Method

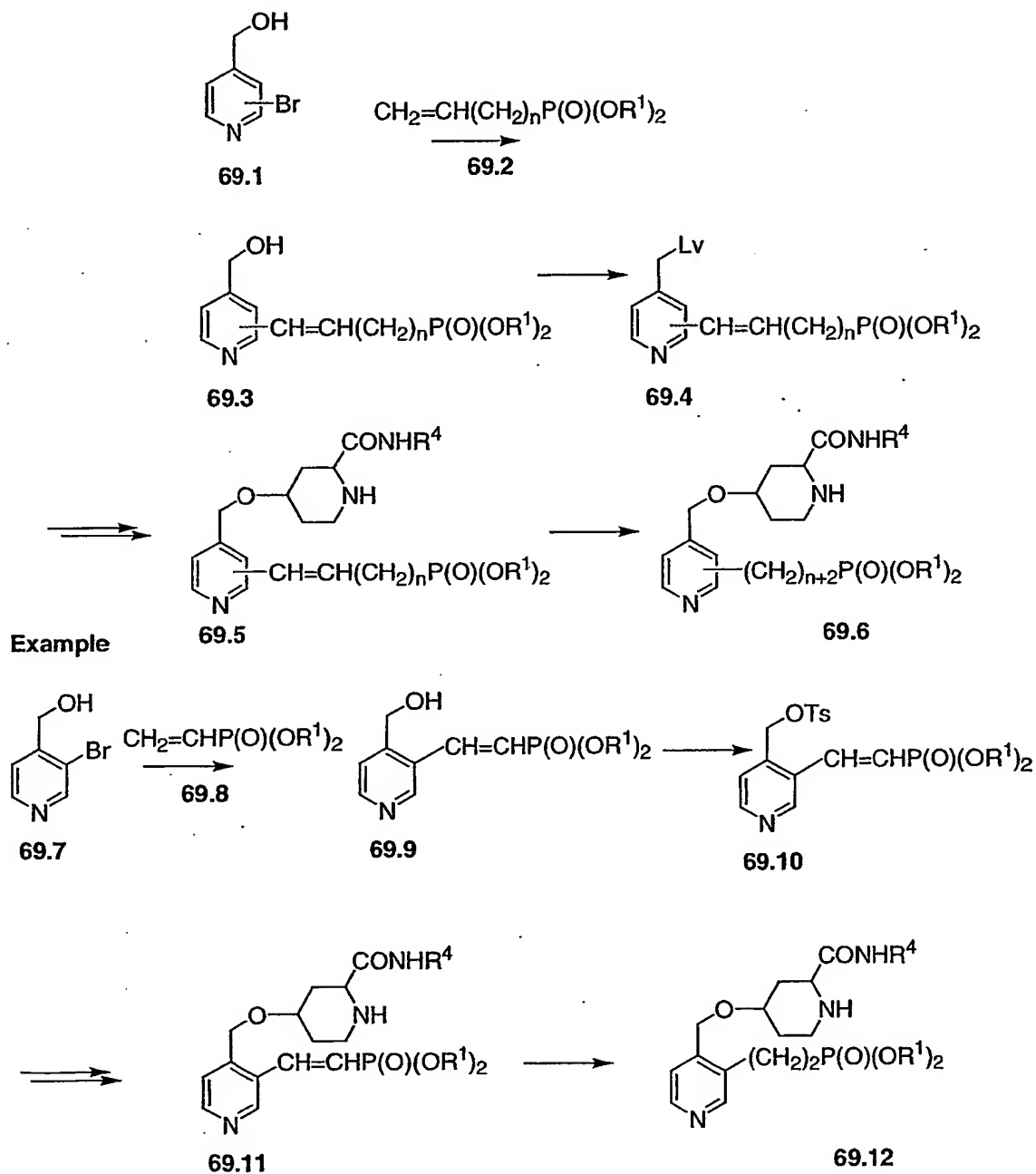


Example



Scheme 69

Method



General applicability of methods for introduction of phosphonate substituents.

The procedures described herein for the introduction of phosphonate moieties are, with appropriate modifications, transferable to different chemical substrates. For example, the methods described above for the introduction of phosphonate groups into the quinoline-2-carboxylic moiety (Schemes 24-27), can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the phenylalanine, thiophenol, tert-butylamine and decahydroisoquinoline moieties. Similarly, the methods described above for the introduction of phosphonate groups into the phenylalanine moiety (Schemes 28-34), the thiophenol moiety (Schemes 35-44) the tert-butylamine moiety (Schemes 45-48), decahydroisoquinoline moiety (Schemes 48a-52), dimethylphenoxyacetic acids (Schemes 56 - 61), benzyl carbamates (Schemes 62 - 65) and pyridines (Schemes 66 - 69) can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the quinoline-2-carboxylic acid component.

15 Preparation of (Pyridin-3-yloxy)-acetic acids incorporating phosphonate moieties.

Scheme 70 illustrates two alternative methods by means of which (pyridin-3-yloxy)-acetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the pyridyl moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed (Pyridin-3-yloxy)-acetic acid intermediate. In the first sequence, a substituted 3-hydroxypyridine 70.1, in which the substituent B is a precursor to the group link-P(O)(OR¹)₂, and in which the aryl hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound 70.2. Methods for the conversion of the substituent B into the group link-P(O)(OR¹)₂ are described in Schemes 25 - 75.

The protected aryl hydroxyl group present in the phosphonate-containing product 70.2 is then deprotected, using methods described below, to afford the phenol 70.3.

The product 70.3 is then transformed into the corresponding (pyridin-3-yloxy) acetic acid 70.4, in a two step procedure. In the first step, the phenol 70.3 is reacted with an ester of bromoacetic acid 70.9, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of aryl

hydroxyl groups to afford aryl ethers is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the aryl reagent and the alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent
5 such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol **70.3** and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described in U.S. Patent 5,914,332, to afford the ester **70.4**.

The thus-obtained ester **70.4** is then hydrolyzed to afford the carboxylic acid **70.5**. The
10 methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group, methods for hydrolysis are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

15 Preferably, the ester product **70.4** which R is ethyl is hydrolyzed to the carboxylic acid **70.5** by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in U.S. Patent 5,914,332.

Alternatively, an appropriately substituted 3-hydroxypyridine **70.6**, in which the substituent B is a precursor to the group $\text{link-P(O)(OR}^1\text{)}_2$, is transformed into the corresponding acetic acid
20 ester **70.7**. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol **70.3** into the ester **70.4**.

The acetic acid ester **70.7** is then converted into the carboxylic acid **70.5** using the 2 step procedure shown above, involving transformation of the group B into the group $\text{link-P(O)(OR}^1\text{)}_2$ followed by ester hydrolysis of the acetic acid ester. The group B which is
25 present in the ester **70.7** may be transformed into the group $\text{link-P(O)(OR}^1\text{)}_2$ either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes **70-75** illustrate the preparation of (Pyridin-3-yloxy)-acetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of
30 acetic esters acids **70.7**, with, if appropriate, modifications made according to the knowledge of one skilled in the art.

Scheme 71 depicts the preparation of (pyridin-3-yloxy) acetic acids incorporating a phosphonate group linked to the pyridyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected halo-substituted 3-hydroxypyridine 71.1 is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate 71.2. The coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl halide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product 71.3 is converted, using the procedures described above, (Scheme 70) into the corresponding (pyridin-3-yloxy) acetic acid 71.4. Alternatively, the olefinic product 71.3 is reduced to afford the saturated derivative 71.5. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or diimide. Following the reduction reaction, the product 71.5 is converted, as described above, (Scheme 70) into the corresponding (pyridin-3-yloxy) acetic acid 71.6.

For example, 2-iodo-5-hydroxy pyridine 71.7, prepared as described in J. Org. Chem., 1990, 55, 18, p. 5287, is converted into the tert-butyldimethylsilyl ether 71.8, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product 71.8 is reacted with an equimolar amount of a dialkyl allyl phosphonate 71.9, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°C, to produce the coupled product 71.10. Alternatively see J. Med. Chem. 1999, 42, 4, p. 669 for alternative conditions for this reaction. The silyl group is removed, for example by the treatment of the ether 71.10 with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol 71.11. This compound is converted, employing the procedures described above, (Scheme 70) into the corresponding (pyridin-3-yloxy) acetic acid 71.12. Alternatively, the unsaturated compound 71.11 is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog 71.13. This

compound is converted, employing the procedures described above, (Scheme 70) into the corresponding (pyridin-3-yloxy) acetic acid 71.14.

Using the above procedures, but employing, in place of 2-iodo-5-hydroxy pyridine 71.7, different iodo or bromohydroxypyridines 71.1, and/or different dialkyl alkenyl phosphonates 71.2, the corresponding products 71.4 and 71.6 are obtained.

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described above (Scheme 54).

Scheme 72 illustrates the preparation of phosphonate-containing analogs of (pyridin-3-yloxy) acetic acids in which the phosphonate moiety is attached to the pyridine ring by means of a heteroatom and an alkyl chain. In this procedure, a suitably protected 2-halo-5-hydroxypyridine, (see Scheme 71) is subjected to a nucleophilic displacement reaction with a dialkyl hydroxy, thio or aminoalkyl-substituted alkyl phosphonate 72.2. The preparation of pyridine ethers, thioethers and amines by means of displacement reactions of 2-bromopyridines, by alcohols, thiols and amines is described, for example, in *Heterocyclic Compounds*, Volume 3, R. A. Abramovitch, ed., Wiley, 1975, p. 597, 191, and 41 respectively. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide at ca 100°C in the presence of a base such as potassium carbonate. The displacement product 72.3 is then converted into the hydroxyl derivative 72.4 and then into the (pyridin-3-yloxy) acetic acid phosphonate ester 72.5 using the procedures described above (Scheme 70).

For example, 2-iodo-5-hydroxypyridine 71.7 (Scheme 71) is treated with benzyl bromide in the presence of base such as potassium carbonate as described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p. 266 to give 72.6. The benzyl ether 72.6 is reacted in dimethylformamide solution at ca 80°C with an equimolar amount of a dialkyl mercaptoethyl phosphonate 72.7, prepared as described in *Zh. Obschei Khim.*, 1973, 43, 2364, and potassium carbonate, to yield the thioether product 72.8. The benzyl group is then removed by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.

266ff., to afford the hydroxyl compound 72.9. The product 72.9 is then converted into the (pyridin-3-yloxy) acetic acid phosphonate ester 72.10 using the procedures described above (Scheme 70).

Using the above procedures, but employing, in place of the mercaptoethyl phosphonate 72.7, different hydroxy, mercapto or alkylamino phosphonates 72.2, and/or in place of the pyridine 71.7 different halo pyridines 71.1, the corresponding products 72.5 are obtained.

Scheme 73 illustrates the preparation of phosphonate-containing analogs of (pyridin-3-yloxy) acetic acids in which the phosphonate moiety is directly attached to the pyridine ring. In this procedure, a suitably protected 2-bromo-5-hydroxypyridine 73.1 is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 73.2. The reaction between aryl bromides and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, 70, 1981, and in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°C, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The thus-obtained pyridylphosphonate 73.3 is then converted, as described above (Scheme 72) into the (pyridin-3-yloxy) acetic acid phosphonate ester 73.5.

For example, 3-bromo-5-hydroxypyridine 73.6 (Synchem-OHG) is treated with benzyl bromide in the presence of base such as potassium carbonate as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p. 266 to give 73.7. The product 73.7 is then treated with a dialkylphosphite 73.2 as described above to give the phosphonate 73.8. Employing the conditions described above (Scheme 72) 73.8 is converted in several steps to the (pyridin-3-yloxy) acetic acid phosphonate ester 73.10. Using the above procedures, but employing, in place of the 3-bromopyridine derivative 73.6, different bromopyridines 73.1, and/or different phosphites, the corresponding products 73.5 are obtained.

Scheme 74 illustrates the preparation of (pyridin-3-yloxy) acetic acids incorporating a phosphonate group attached to the pyridyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an hydroxy, thio or amino-substituted 3-hydroxy pyridine 74.1, protected at the 3-hydroxyl position is reacted, in the presence of a base such as, for example, potassium carbonate, and optionally in

the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate 74.6. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°C. The product of the alkylation reaction, 74.2 is then converted, as described above for converting 72.3 to 5 72.5 (Scheme 72) into the acid 74.5.

Alternatively, the protected pyridine 74.7 is converted to the acetic acid ester derivative 74.8 using the procedures described above in Scheme 70. The acetic acid ester 74.8, is then deprotected following the procedures described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, ch 3,6, and 7, and the product 10 treated with a dialkyl bromoalkyl phosphonate 74.6 to give 74.4. The ester 74.4 is converted to the acid 74.5 using the procedures described above (Scheme 70).

For example, 3-benzyloxy, 5-hydroxy pyridine 74.10, prepared as described Bioorg and Med. Chem. Lett. 1998, p. 2797, is converted to the ester 74.11 by treatment with ethylbromoacetate as described above (Scheme 70). The benzyl group is removed, for 15 example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the hydroxy pyridine 74.12. The product 74.12 is reacted in dimethylformamide at ca. 60°C with an equimolar amount of a dialkyl bromobutyl phosphonate 74.14, the preparation of which is described in Synthesis, 20 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the phosphonate ether product 74.13. This compound is converted, employing the procedures described above, (Scheme 70) into the corresponding acid 74.15.

Using the above procedures, but employing, in place of the pyridine 74.10, different hydroxy, thio or aminophenols 74.1, and/or different dialkyl bromoalkyl phosphonates 74.6, the 25 corresponding products 74.5 are obtained.

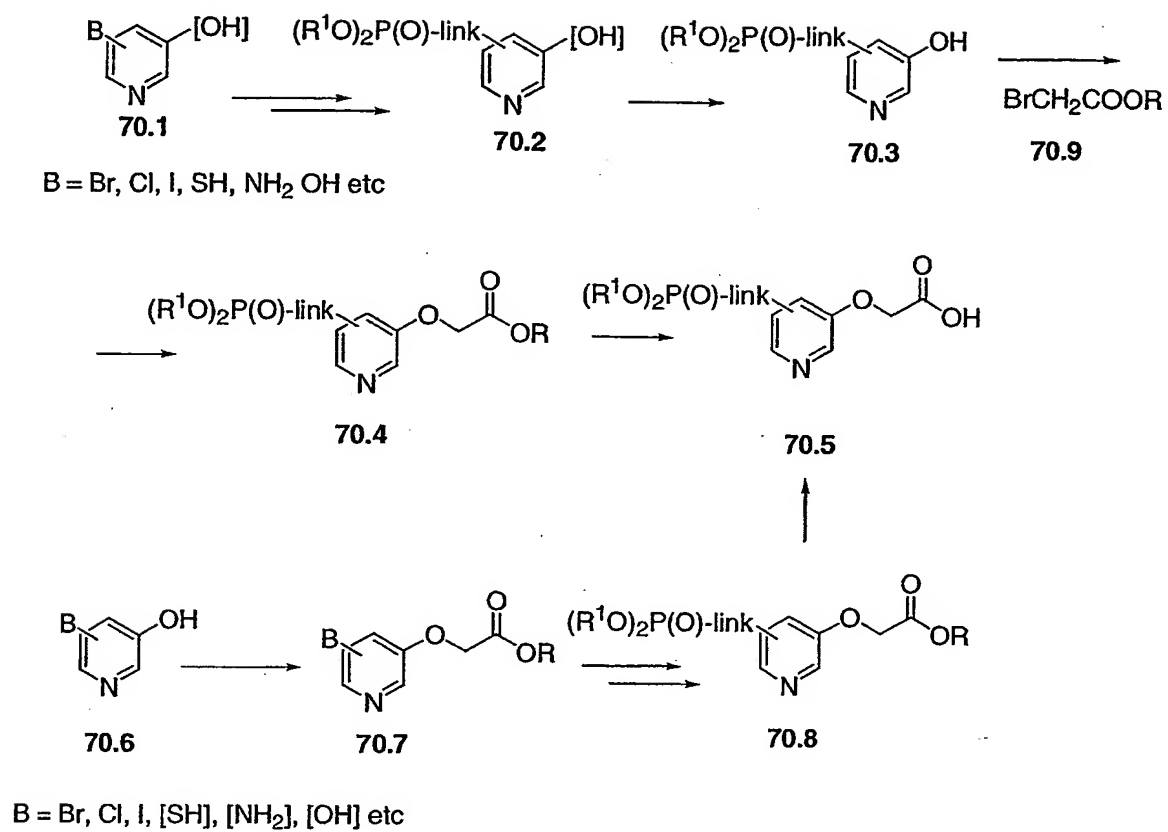
Scheme 75 illustrates the preparation of (Pyridin-3-yloxy)-acetic acids incorporating a phosphonate ester which is attached to the pyridyl group by means of a carbon chain incorporating a nitrogen atom. The compounds 75.4 are obtained by means of a reductive 30 alkylation reaction between hydroxyl protected 3-hydroxypyridyl aldehyde 75.1 and an aminoalkyl phosphonate ester 75.2. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations,

by R. C. Larock, VCH, p. 421. In this procedure, the amine component 75.2 and the aldehyde component 75.1 are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product 75.3. The amination product 75.3 is then deprotected according to procedures described in
5 Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, ch3, and subsequently converted into the (pyridin-3-yloxy) acetic acid compound 75.4, using the alkylation and ester hydrolysis procedures described above (Scheme 70).

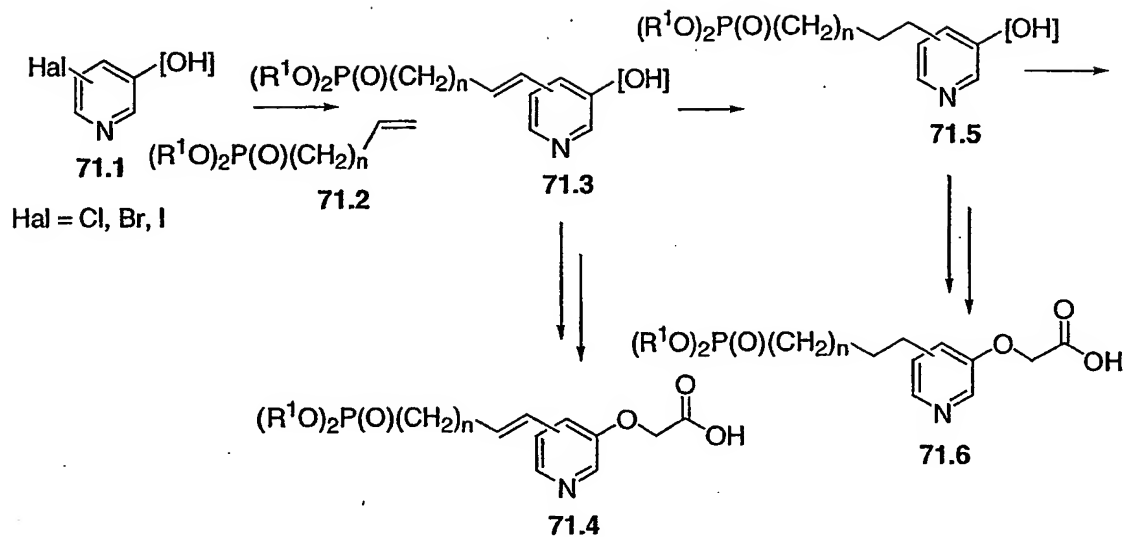
For example, the ester 75.5 (TCI-US) is reacted with benzyl bromide in the presence of base
10 such as potassium carbonate as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p. 266 to give 75.6. The benzyl ether 75.6 is then converted to the aldehyde 75.7 by reaction with DIBAL (see Comprehensive Organic Transformations, by R. C. Larock, 2nd Edition, 1999, p. 1267. for examples). Equimolar amounts of aldehyde 75.7, and a dialkyl aminoethyl phosphonate 75.8, the
15 preparation of which is described in J. Org. Chem., 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in J. Amer. Chem. Soc., 91, 3996, 1969, to afford the amine product 75.9. The benzyl group is then removed by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by
20 R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the hydroxyl compound 75.10. The product 75.10 is then converted into the acetic acid 75.11, as described above (Scheme 70). Using the above procedures, but employing, in place of the aldehyde 75.7, different aldehydes 75.1, and/or different aminoalkyl phosphonates 75.2, the corresponding products 75.4 are obtained.

25

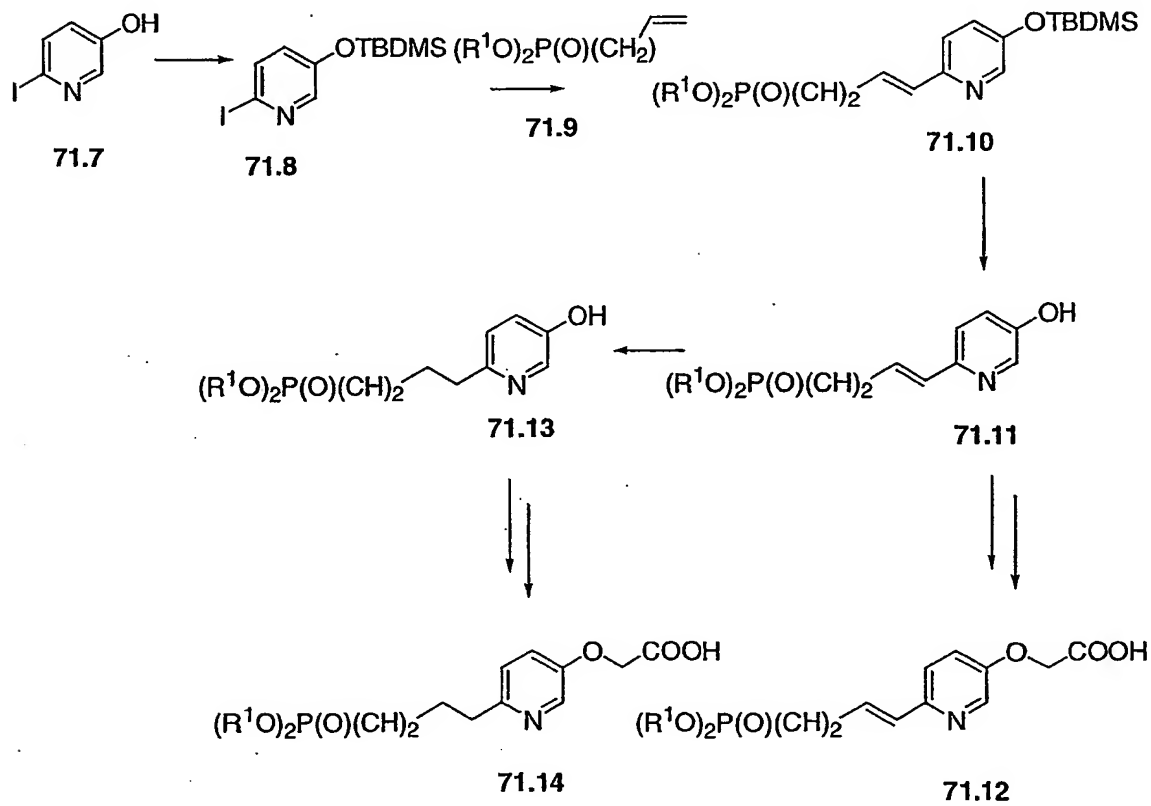
Scheme 70



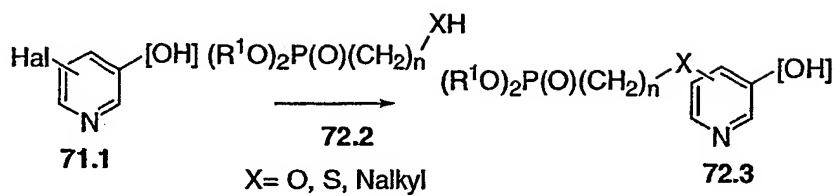
Scheme 71



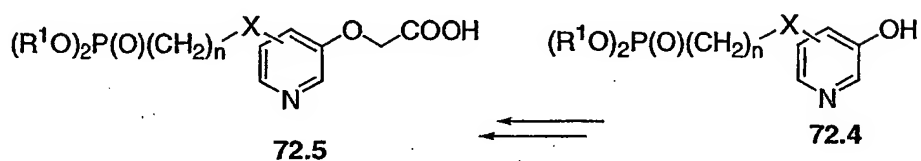
Example



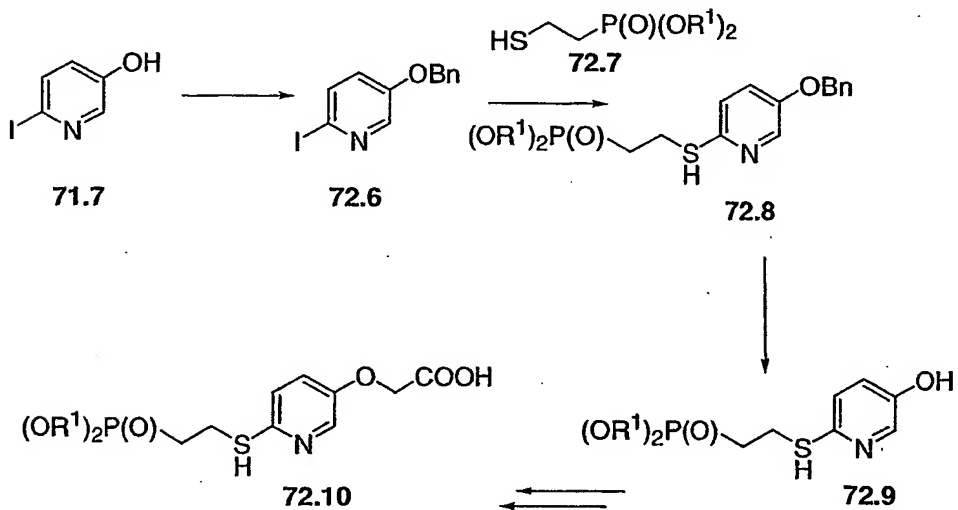
Scheme 72



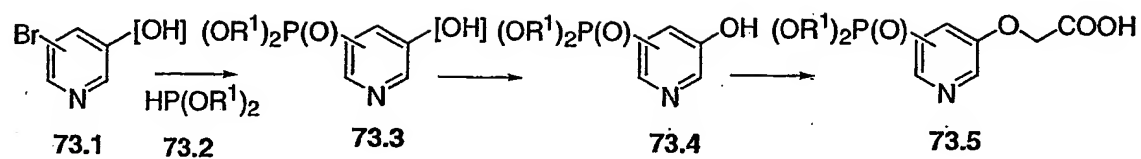
Hal = Cl, Br, I



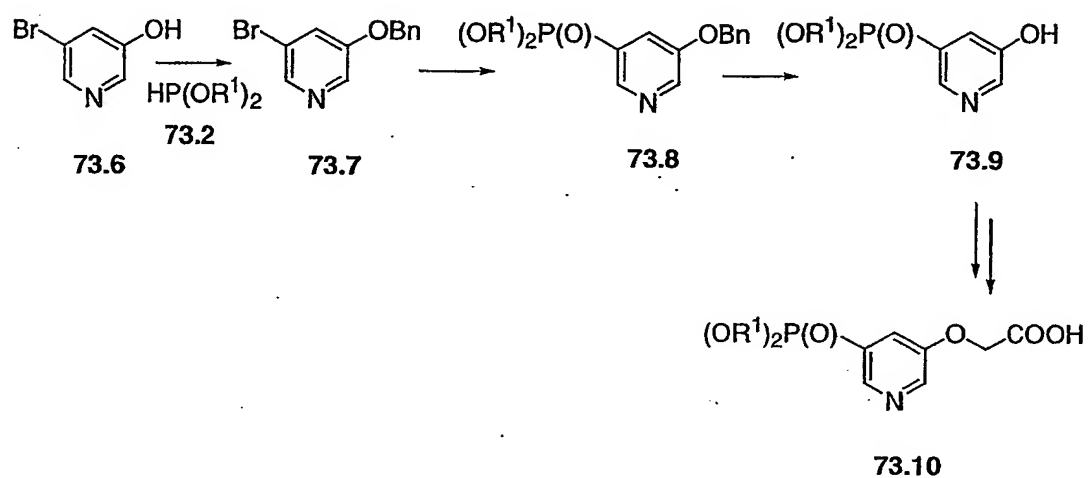
Example



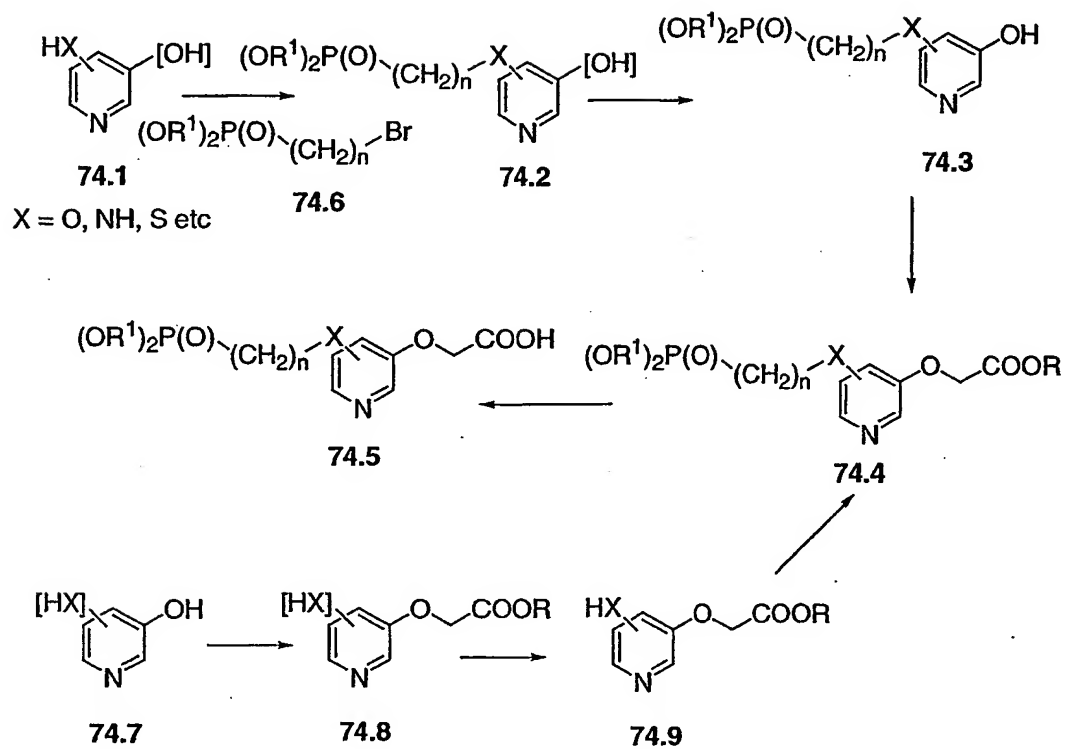
Scheme 73



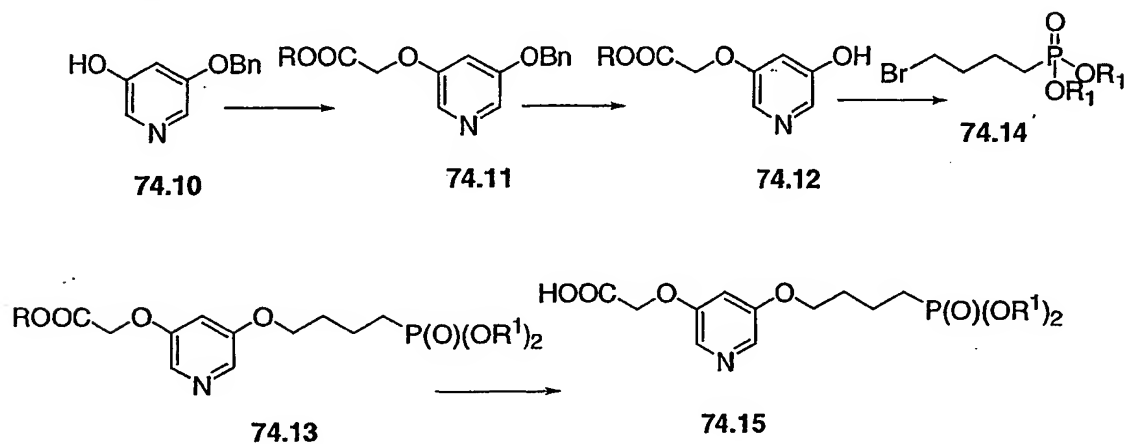
Example



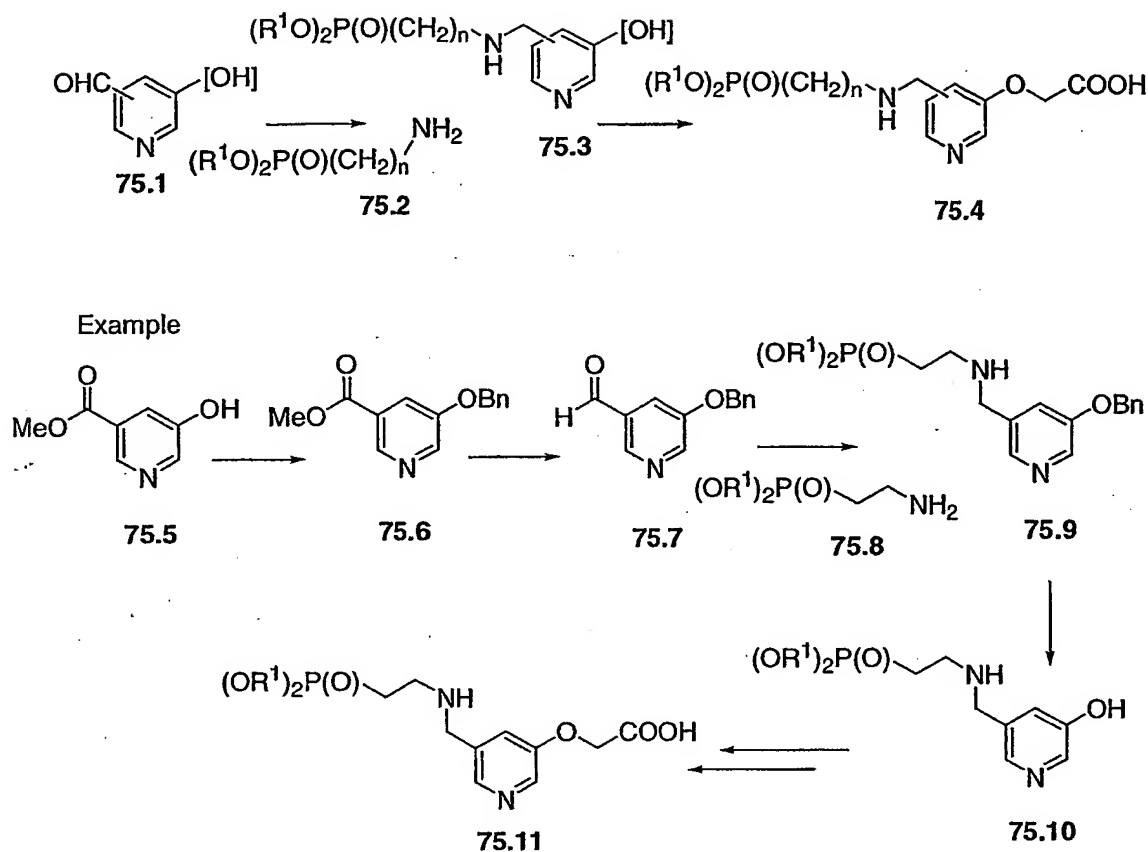
Scheme 74



Example



Scheme 75

Ritonavir-like phosphonate protease inhibitors (RLPPI)

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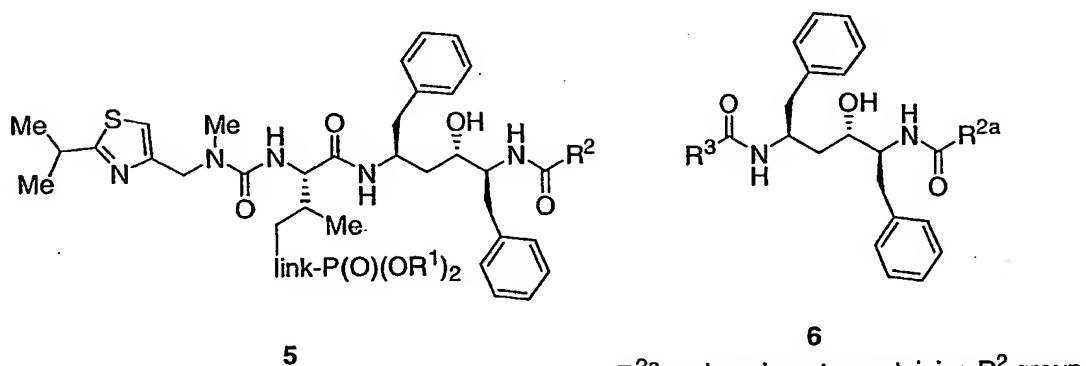
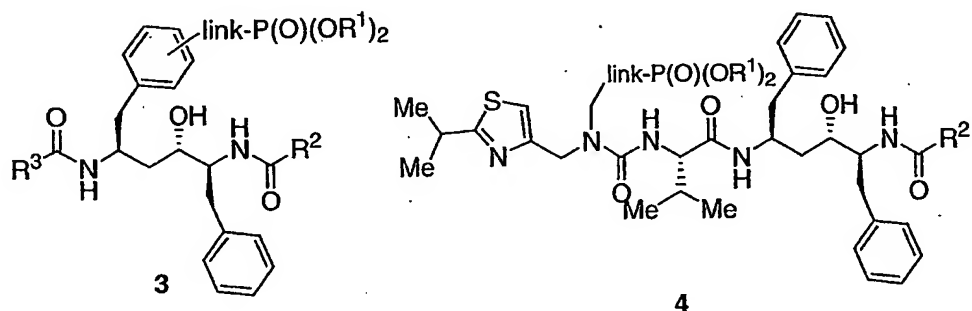
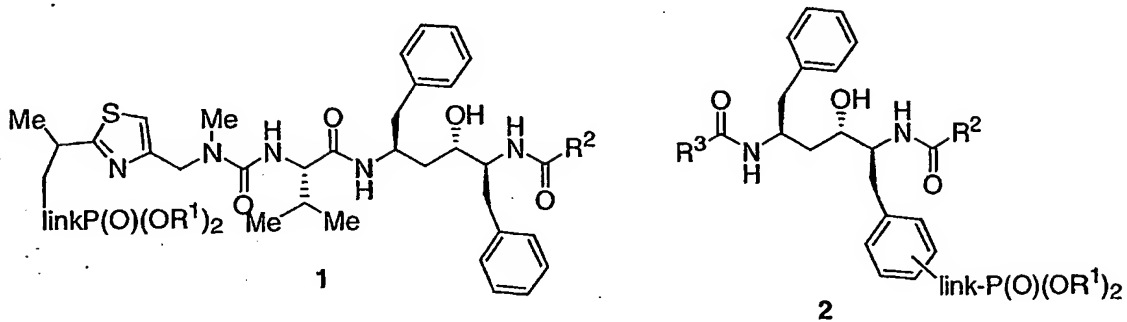
Chemistry for Ritonavir analogs.**Preparation of the intermediate phosphonate esters.**

The structures of the intermediate phosphonate esters 1 to 7, and the structures for the component groups R^1 of this invention are shown in Chart 1. The structures of the components R^2COOH , R^3COOH and R^4 are shown in Charts 2a, 2b and 2c. Specific stereoisomers of some of the structures are shown in Charts 1 and 2; however, all stereoisomers are utilized in the syntheses of the compounds 1 to 7. Subsequent chemical modifications to the compounds 1 to 7, as described herein, permit the synthesis of the final compounds of this invention.

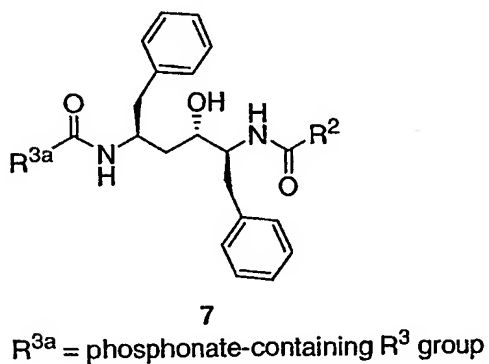
15

The intermediate compounds **1** to **7** incorporate a phosphonate moiety connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **3** and **4** illustrate examples of the linking groups present in the structures **1** – **7**, and in which "etc" refers to the scaffold, e.g., ritonavir.

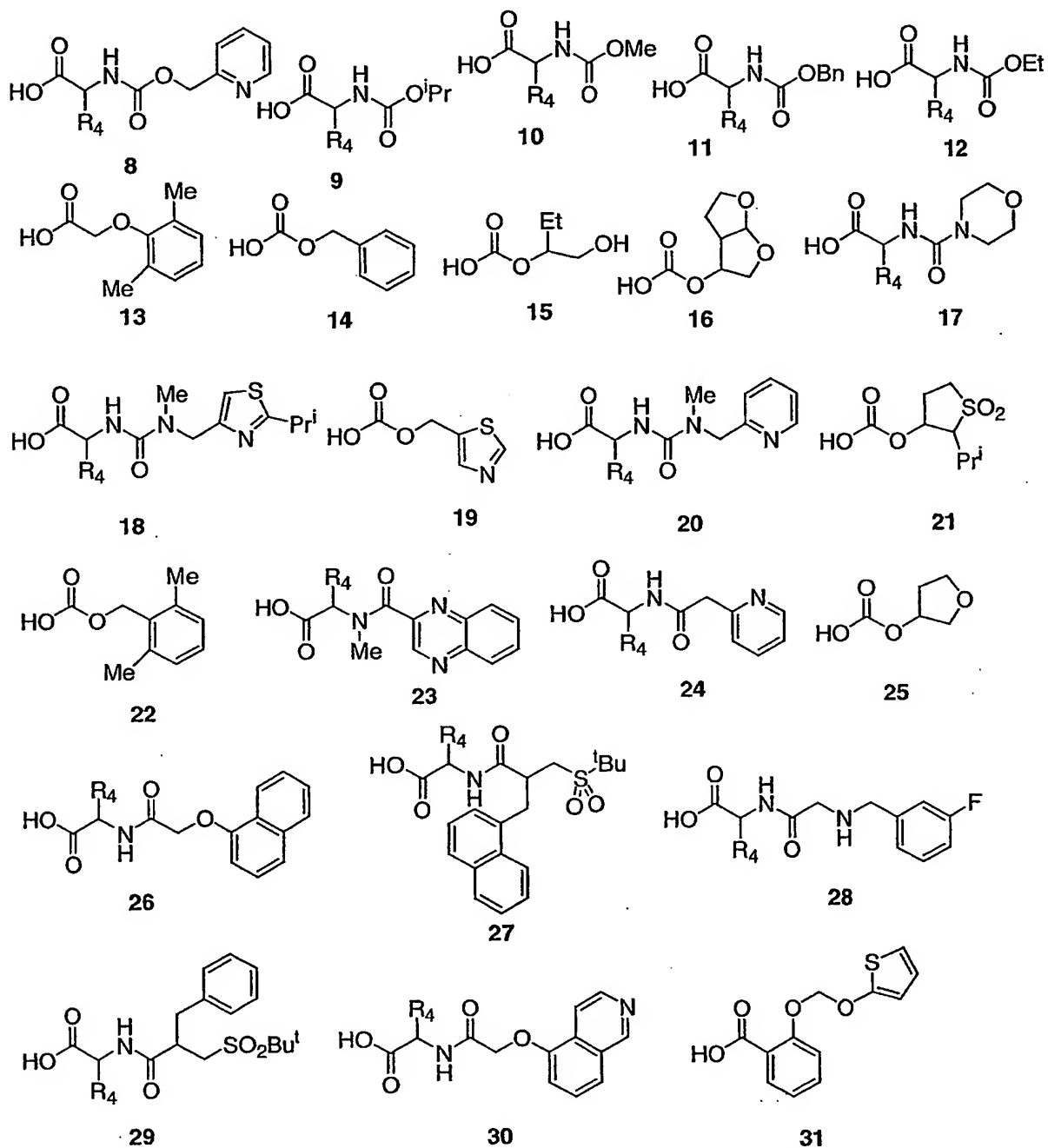
- 5 Schemes **1** - **28** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1**- **5**, and of the intermediate compounds necessary for their synthesis. The preparation of the compounds **6** and **7**, in which the phosphonate moiety is attached to the R^2COOH or R^3COOH group, is also described below.

Chart 1 Structures of the intermediate phosphonate esters 1-7

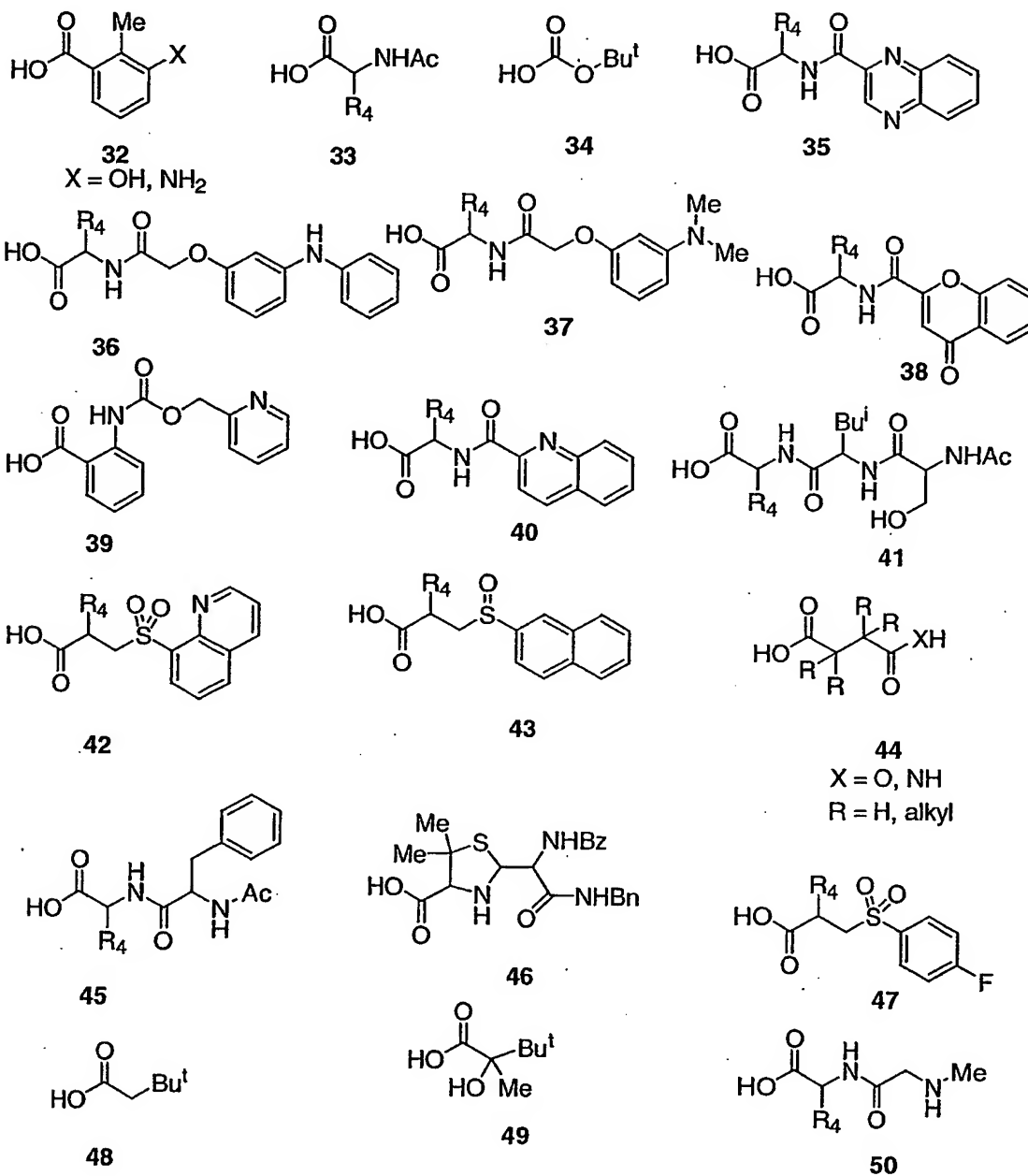
R^{2a} = phosphonate-containing R^2 group



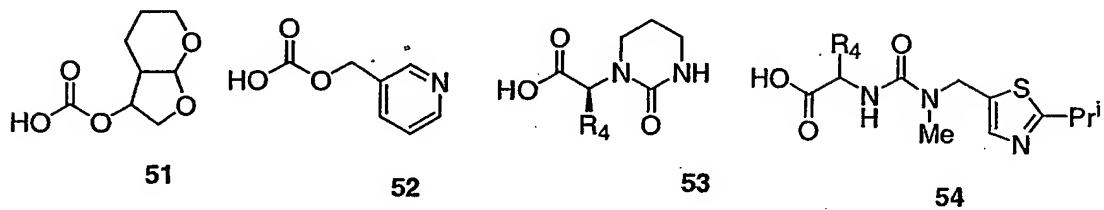
R^1 = H, alkyl, alkenyl, aralkyl, aryl.

Chart 2a Structures of the R²COOH and R³COOH components

R⁴ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

Chart 2b Structures of the R²COOH and R³COOH components

R⁴ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

Chart 2c Structures of the R²COOH and R³COOH components

R⁴ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

Chart 3 Examples of the linking group between the scaffold and the phosphonate moiety.

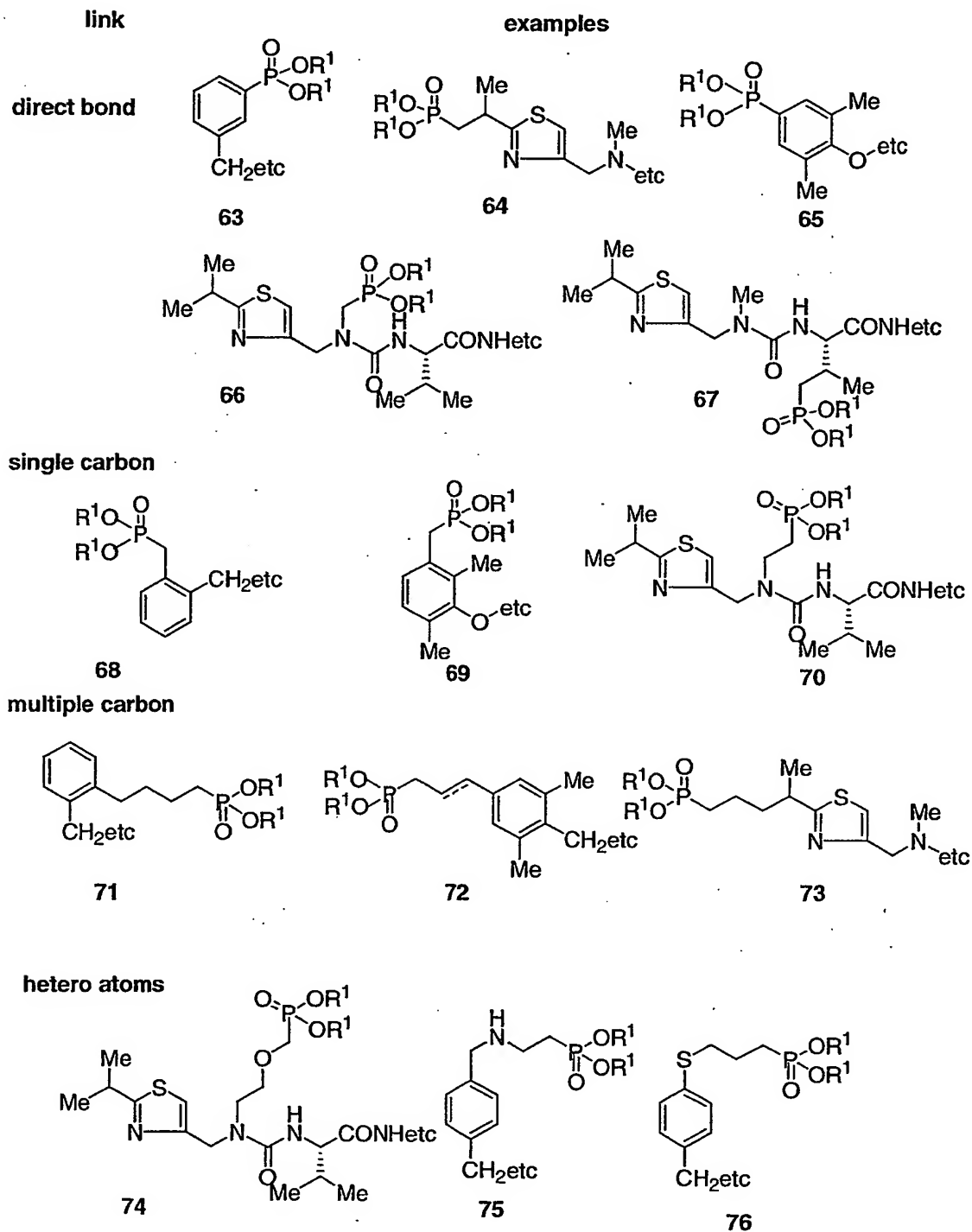
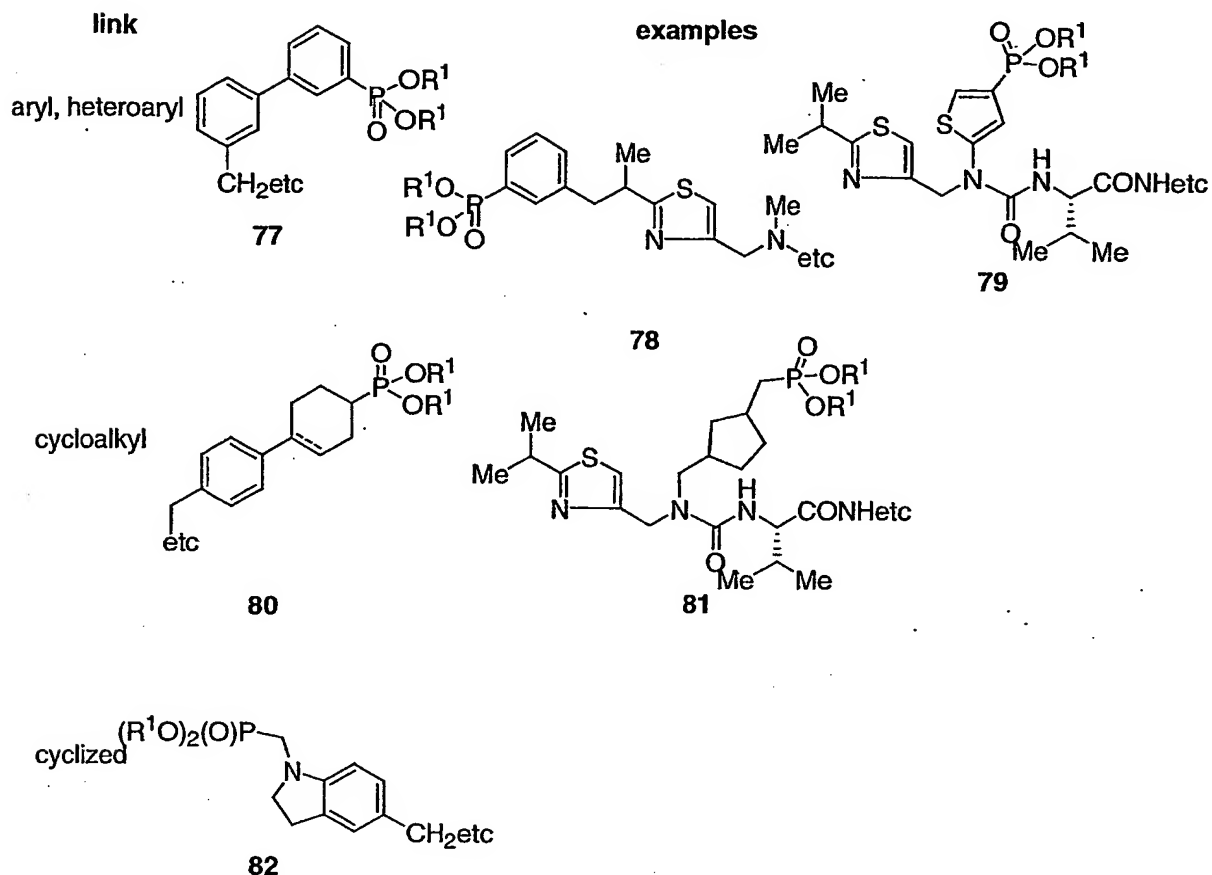


Chart 4 Examples of the linking group between the scaffold and the phosphonate moiety.



Protection of reactive substituents.

5

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate intermediates 1.

Two methods for the preparation of the phosphonate intermediate compounds 1, in which the phosphonate moiety is attached to the isopropyl group of the carboxylic acid reactant 1.5, are shown in Schemes 1 and 2. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme 1, 5-amino-2-dibenzylamino-1,6-diphenyl-hexan-3-ol, 1.1, the preparation of which is described in Org. Process Res. Dev., 1994, 3, 94, is reacted with a carboxylic acid R^2COOH 1.2, or an activated derivative thereof, to produce the amide 1.3.

The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff.

The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, dimethylformamide or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, imidazolid and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid 1.2 is converted into the acid chloride, and the latter compound is reacted with an equimolar amount of the amine 1.1, in an aprotic solvent such as, for example, tetrahydrofuran, at ambient temperature. The reaction is conducted in the presence of an organic base such as triethylamine, so as to afford the amide 1.3.

The N, N-dibenzylamino amide product 1.3 is then transformed into the free amine compound 1.4 by means of a debenzylation procedure. The deprotection of N-benzyl amines is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 365. The transformation can be effected under

reductive conditions, for example by the use of hydrogen or a hydrogen donor, in the presence of a palladium catalyst, or by treatment of the N-benzyl amine with sodium in liquid ammonia, or under oxidative conditions, for example by treatment with 3-chloroperoxybenzoic acid and ferrous chloride.

- 5 Preferably, the N, N-dibenzyl compound 1.3 is converted into the amine 1.4 by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic ammonium formate and 5% palladium on carbon catalyst, at ca. 75°C for ca. 6 hours, for example as described in U.S. Patent 5,914,332.

- The thus-obtained amine 1.4 is then transformed into the amide 1.6 by reaction with the
10 carboxylic acid 1.5, or an activated derivative thereof, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto. Preparations of the carboxylic acids 1.5 are described below, Schemes 13 - 15. The amide-forming reaction is conducted under similar conditions to those described above for the preparation of the amide 1.3.

- Preferably, the carboxylic acid is converted into the acid chloride, and the acid chloride is
15 reacted with the amine 1.4 in a solvent mixture composed of an organic solvent such as ethyl acetate, and water, in the presence of a base such as sodium bicarbonate, for example as described in Org. Process Res. Dev., 2000, 4, 264, to afford the amide product 1.6.

- Scheme 2 illustrates an alternative method for the preparation of the phosphonate-containing diamides 1. In this procedure, 2-phenyl-1-[4-phenyl-2-(1-vinyl-propenyl)-
20 [1,3,2]oxazaborinan-6-yl]-ethylamine 2.1, the preparation of which is described in WO 9414436, is reacted with the carboxylic acid R²COOH 1.2, or an activated derivative thereof, to afford the amide product 2.2. The reaction is effected employing the same conditions as were described above for the preparation of the amide 1.3. Preferably, equimolar amounts of the acid chloride derived from the carboxylic acid 1.2 is reacted with the amine 2.1 in a polar
25 aprotic solvent such as tetrahydrofuran or dimethylformamide, at from ambient temperature to about -60°C, in the presence of an organic or inorganic base, to produce the amide 2.2. The product is then reacted with the carboxylic acid 1.5, or an activated derivative thereof, to afford the amide 1.6. The amide-forming reaction is conducted under similar conditions to those described above for the preparation of the amide 1.3. Preferably, the acid 1.5 and the
30 amine 2.2 are reacted in the presence of hydroxybenztriazole, and N-ethyl-N'-dimethylaminopropyl carbodiimide, in tetrahydrofuran at ambient temperature, as described in U.S. Patent 5,484,801, to yield the amide 1.6.

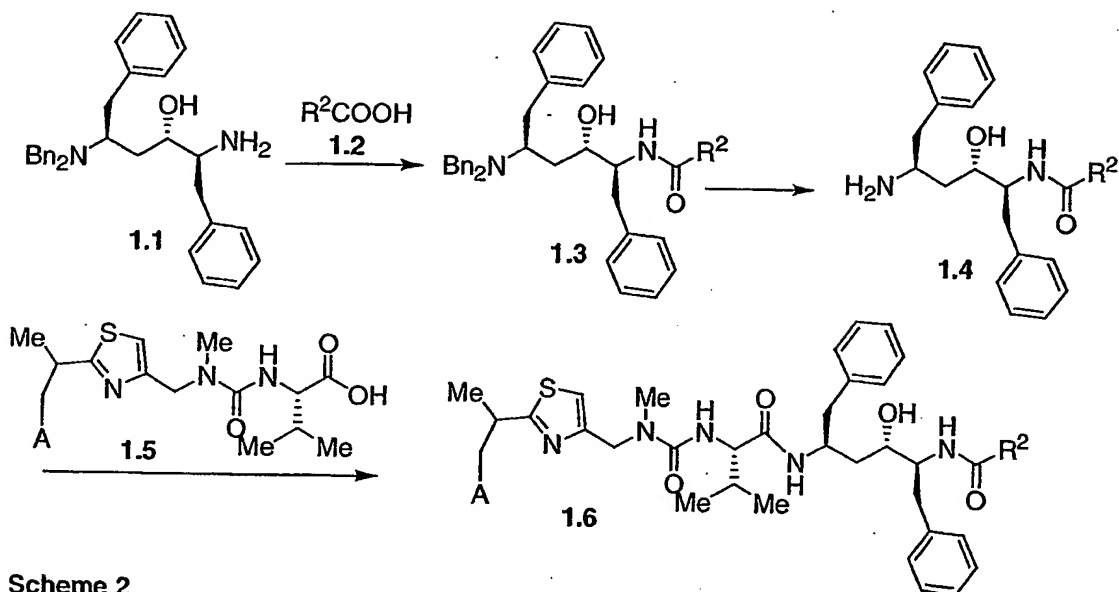
The reactions illustrated in Schemes 1 and 2 illustrate the preparation of the compounds 1.6 in which A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH, as described below. Scheme 3 depicts the conversion of

5 the compounds 1.6 in which A is OH, SH, NH, as described below, into the compounds 1 in which A is the group $\text{link-P(O)(OR}^1\text{)}_2$. Procedures for the conversion of the group A into the group $\text{link-P(O)(OR}^1\text{)}_2$ are described below, (Schemes 16-26).

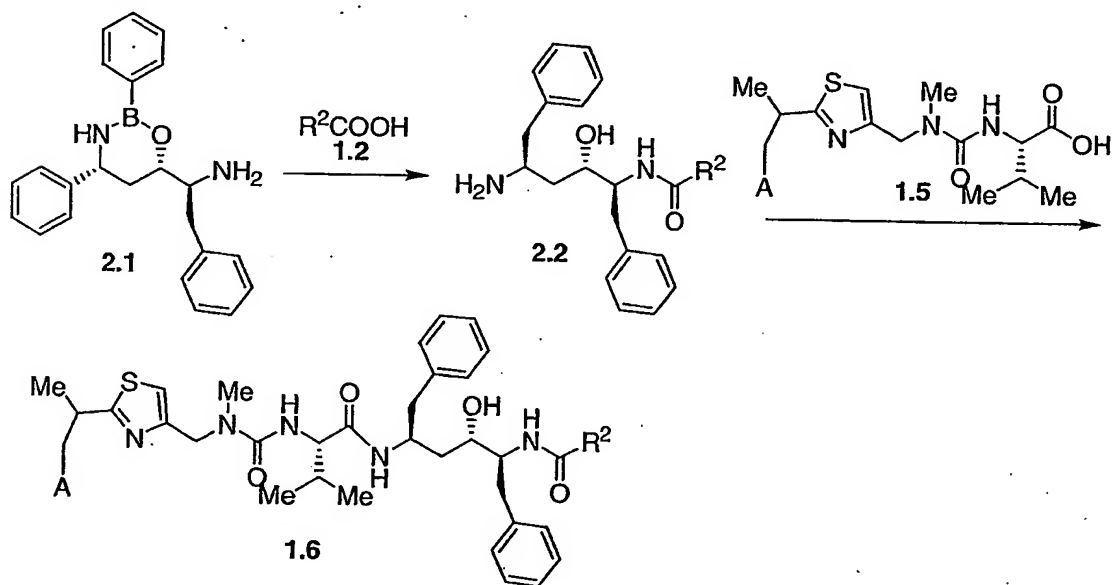
In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations.

10 The transformations, and the methods by which they are accomplished, are described below, (Scheme 27)

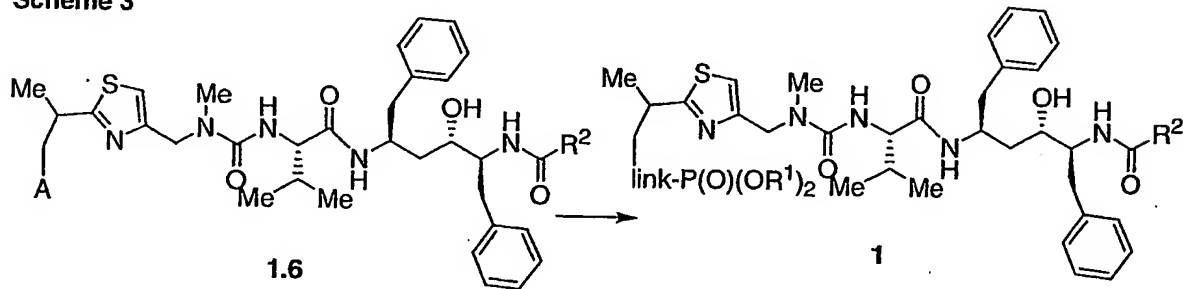
Scheme 1



Scheme 2



Scheme 3



Preparation of the phosphonate intermediates 2.

Two methods for the preparation of the phosphonate intermediate compounds 2 are shown in
5 Schemes 4 and 5. The selection of the route to be employed for a given compound is made
after consideration of the substituents which are present, and their stability under the reaction
conditions required.

As depicted in Scheme 4, the tribenzylated phenylalanine derivative 4.1, in which the
substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor thereto, as described below, is
10 reacted with the anion 4.2 derived from acetonitrile, to afford the ketonitrile 4.3. Preparations
of the tribenzylated phenylalanine derivatives 4.1 are described below, Schemes 16-18.

The anion of acetonitrile is prepared by the treatment of acetonitrile with a strong base, such
as, for example, lithium hexamethyldisilylazide or sodium hydride, in an inert organic solvent
such as tetrahydrofuran or dimethoxyethane, as described, for example, in U.S. Patent
15 5,491,253. The solution of the acetonitrile anion 4.2, in an aprotic solvent such as
tetrahydrofuran, dimethoxyethane and the like, is then added to a solution of the ester 4.1 at
low temperature, to afford the coupled product 4.3.

Preferably, a solution of ca. two molar equivalent of acetonitrile, prepared by the addition of
ca. two molar equivalent of sodium amide to a solution of acetonitrile in tetrahydrofuran at -
20 40°C, is added to a solution of one molar equivalent of the ester 4.1 in tetrahydrofuran at -
40°C, as described in J. Org. Chem., 1994, 59, 4040, to produce the ketonitrile 4.3.

The above-described ketonitrile compound 4.3 is then reacted with an organometallic benzyl
reagent 4.4, such as a benzyl Grignard reagent or benzyllithium, to afford the ketoenamine 4.5.
The reaction is conducted in an inert aprotic organic solvent such as diethyl ether,
25 tetrahydrofuran or the like, at from -80°C to ambient temperature.

Preferably, the ketonitrile 4.3 is reacted with three molar equivalents of benzylmagnesium
chloride in tetrahydrofuran at ambient temperature, to produce, after quenching by treatment
with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59,
4040, the ketoenamine 4.5.

30 The ketoenamine 4.5 is then reduced, in two stages, via the ketoamine 4.6, to produce the
amino alcohol 4.7. The transformation of the ketoenamine 4.5 to the aminoalcohol 4.7 can be

effected in one step, or in two steps, with or without isolation of the intermediate ketoamine 4.6, as described in U.S. Patent 5,491,253.

For example, the ketoenamine 4.5 is reduced with a boron-containing reducing agent such as sodium borohydride, sodium cyanoborohydride and the like, in the presence of an acid such as methanesulfonic acid, as described in J. Org. Chem., 1994, 59, 4040, to afford the ketoamine 4.6. The reaction is performed in an ethereal solvent such as, for example, tetrahydrofuran or methyl tert-butyl ether. The latter compound is then reduced with sodium borohydride-trifluoroacetic acid, as described in U.S. Patent 5,491,253, to afford the aminoalcohol 4.7. Alternatively, the ketoenamine 4.5 can be reduced to the aminoalcohol 4.7 without isolation of the intermediate ketoamine 4.6. In this procedure, described in U.S. Patent 5,491,253, the ketoenamine 4.5 is reacted with sodium borohydride-methanesulfonic acid, in an ethereal solvent such as dimethoxyethane and the like. The reaction mixture is then treated with a quenching agent such as triethanolamine, and the procedure is continued by the addition of sodium borohydride and a solvent such as dimethyl formamide or dimethylacetamide or the like, to afford the aminoalcohol 4.7.

The aminoalcohol 4.7 is converted into the amide 4.9 by reaction with the acid R^3COOH 4.8, or an activated derivative thereof, to produce the amide 4.9. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.6.

The dibenzylated amide product 4.9 is deprotected to afford the free amine 4.10. The conditions for the debenzylation reaction are the same as those described above for the deprotection of the dibenzyl amine 1.3 to yield the amine 1.4, (Scheme 1).

The amine 4.10 is then reacted with the carboxylic acid R^2COOH 1.2, or an activated derivative thereof, to produce the amide 4.11. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.6.

Alternatively, the amide 4.11 can be prepared by means of the sequence of reactions illustrated in Scheme 5.

In this sequence, the tribenzylated amino acid derivative 4.1 is converted, by means of the reaction sequence shown in Scheme 4 into the dibenzylated amine 4.7. This compound is then converted into a protected derivative, for example the tert-butoxycarbonyl (BOC) derivative 5.1. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990,

p. 327. For example, the amine can be reacted with di-tert-butoxycarbonylanhydride (BOC anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), and the like.

Preferably, the amine is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess
5 potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in U.S. Patent 5,914,3332, to yield the BOC-protected product 5.1.

The N-benzyl protecting groups are then removed from the amide product 5.1 to afford the free amine 5.2. The conditions for this transformation are similar to those described above for the preparation of the amine 1.4, (Scheme 1).

10 Preferably, the N, N-dibenzyl compound 5.1 is converted into the amine 5.2 by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic ammonium formate and 5% palladium on carbon catalyst, at ca. 75°C for ca. 6 hours, for example as described in U.S. Patent 5,914,332.

The amine compound 5.2 is then reacted with the carboxylic acid R^2COOH 1.2, or an
15 activated derivative thereof, to produce the amide 5.3. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.6, to afford the amide product 5.3.

The latter compound is then converted into the amine 5.4 by removal of the BOC protecting group. The removal of BOC protecting groups is described, for example, in Protective
20 Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preferably, the BOC group is removed by treatment of the substrate 5.3 with trifluoroacetic
25 acid in dichloromethane at ambient temperature, for example as described in U.S. Patent 5,914,232, to afford the free amine product 5.4.

The free amine thus obtained is then reacted with the carboxylic acid R^3COOH 4.8, or an activated derivative thereof, to produce the amide 4.11. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.6.

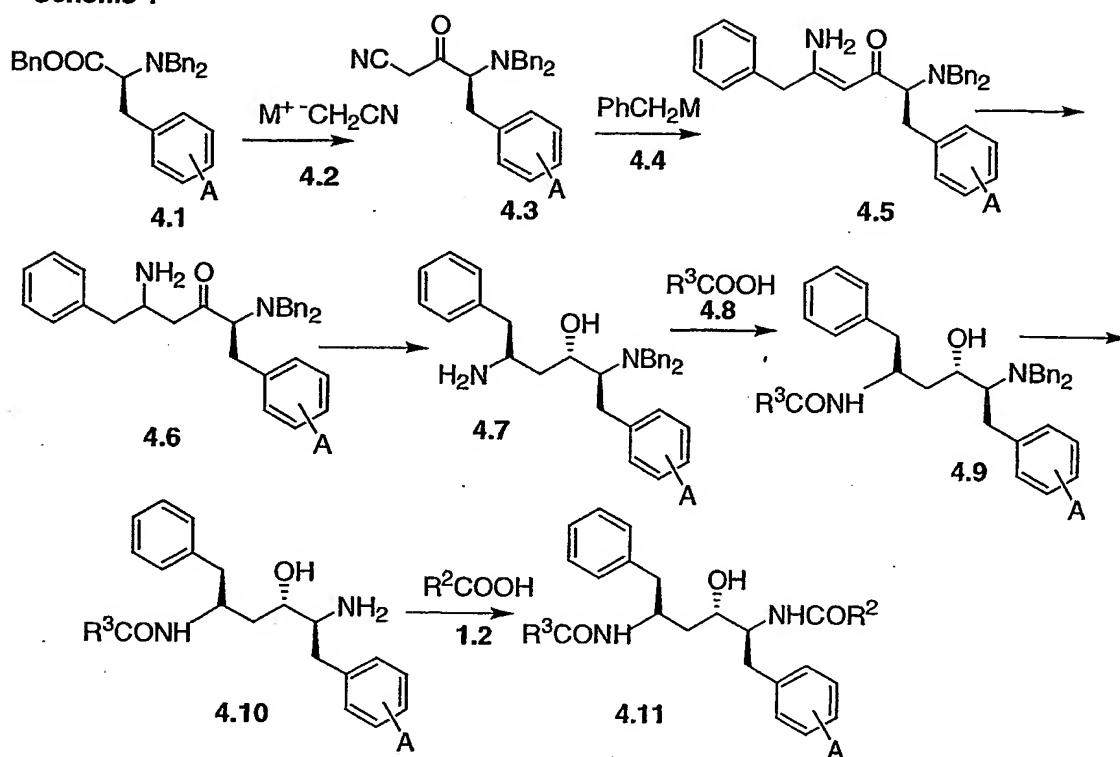
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The reactions shown in Schemes 4 and 5 illustrate the preparation of the compounds 4.11 in which A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor thereto, such as, for example,

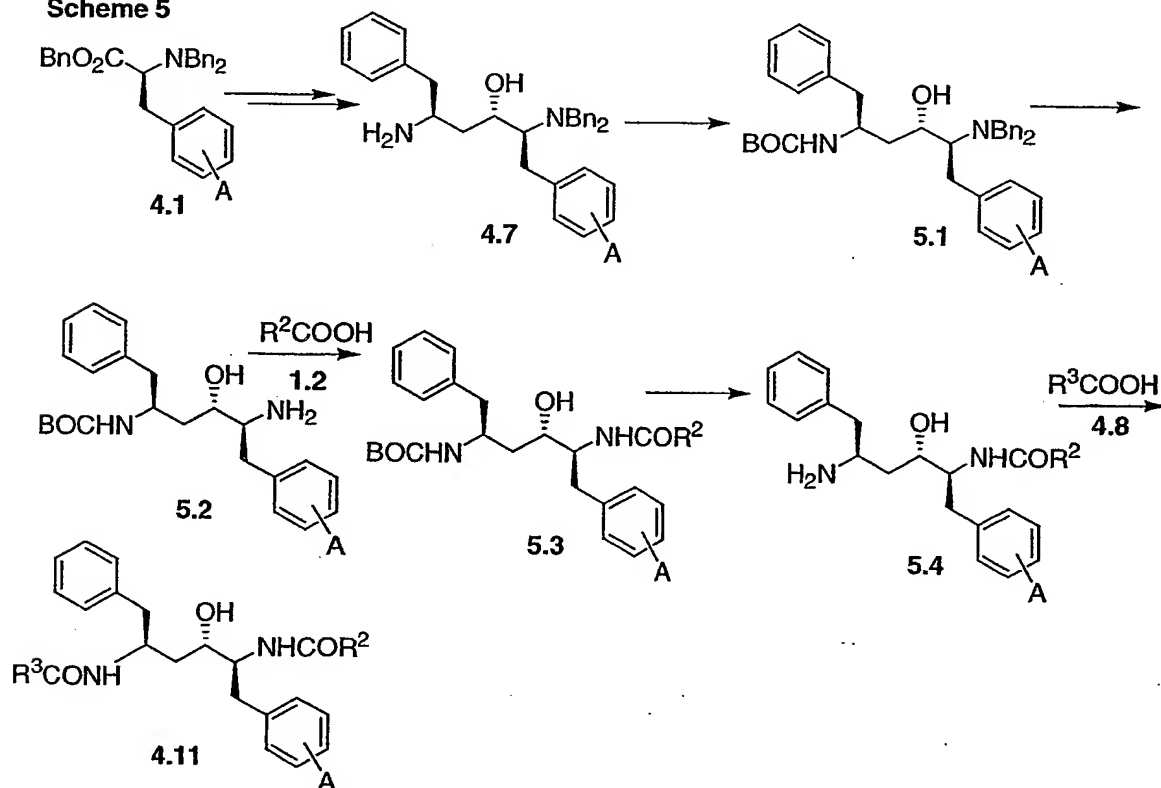
optionally protected OH, SH, NH, as described below. Scheme 6 depicts the conversion of the compounds 4.11 in which A is OH, SH, NH, as described below, into the compounds 2. Procedures for the conversion of the group A into the group $\text{link-P(O)}(\text{OR}^1)_2$ are described below, (Schemes 16-26).

5

Scheme 4



Scheme 5



Preparation of the phosphonate intermediates 3.

The phosphonate ester intermediate compounds 3 can be prepared by two alternative methods, illustrated in Schemes 7 and 8. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme 7, 4-dibenzylamino-3-oxo-5-phenyl-pentanenitrile 7.1, the preparation of which is described in J. Org. Chem., 1994, 59, 4040, is reacted with a substituted benzylmagnesium halide reagent 7.2, in which the group B is a substituent, protected if appropriate, which can be converted, during or after the sequence of reactions shown in Scheme 7, into the moiety link-P(O)(OR)^1_2 . Examples of the substituent B are Br, [OH], [SH], [NH₂] and the like; procedures for the transformation of these groups into the phosphonate moiety are shown below in Schemes 16-26. The conditions for the reaction between the benzylmagnesium halide and the ketonitrile are similar to those described above for the preparation of the ketoenamine 4.5 (Scheme 4).

Preferably, the ketonitrile 7.1 is reacted with three molar equivalents of the substituted benzylmagnesium chloride 7.2 in tetrahydrofuran at ambient temperature, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine 7.3.

The thus-obtained ketoenamine 7.3 is then transformed, via the intermediate compounds 7.4, 7.5, 7.6, and 7.7 into the diacylated carbinol 7.8. The conditions for each step in the conversion of the ketoenamine 7.3 to the diacylated carbinol 7.8 are the same as those described above (Scheme 4) for the transformation of the ketoenamine 4.5 into the diacylated carbinol 4.11.

The diacylated carbinol 7.8 is then converted into the phosphonate ester 3, using procedures illustrated below in Schemes 16-26.

Alternatively, the phosphonate esters 3 can be obtained by means of the reactions illustrated in Scheme 8. In this procedure, the amine 7.5, the preparation of which is described above, (Scheme 7) is converted into the BOC derivative 8.1. The conditions for the introduction of

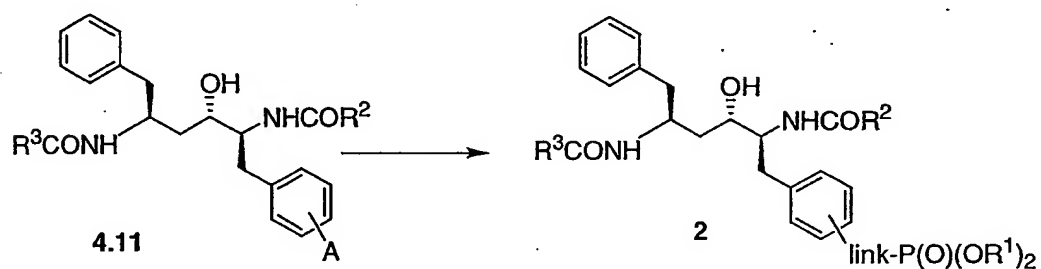
the BOC group are similar to those described above for the protection of the amine 5.1, (Scheme 5).

Preferably, the amine is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in U.S. Patent 5,914,332, to yield the BOC-protected product 8.1.

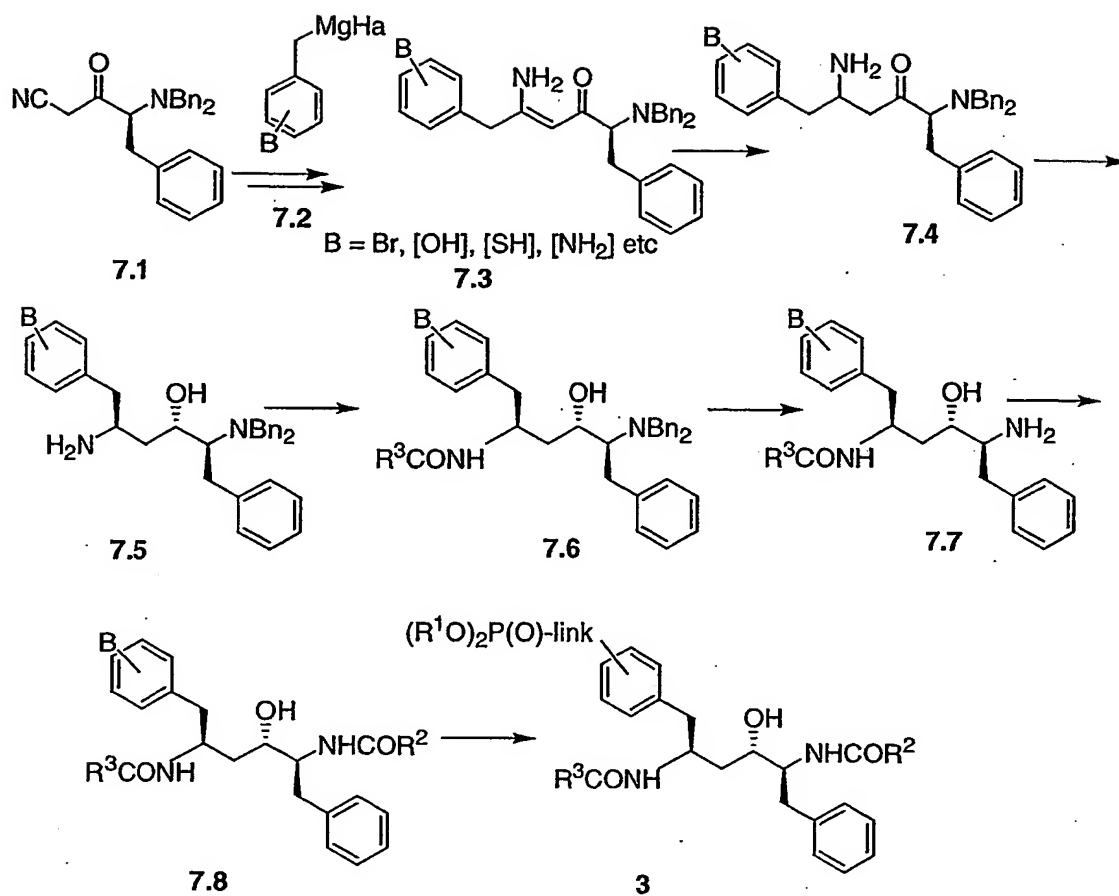
The BOC-protected amine 8.1 is then converted, via the intermediates 8.2, 8.3 and 8.4 into the diacylated carbinol 8.5. The reaction conditions for this sequence of reactions are similar to those described above for the transformation of the BOC-protected amine 5.1 into the diacylated carbinol 5.4 (Scheme 5).

- 10 The diacylated carbinol 8.5 is then converted into the phosphonate ester 3, using procedures illustrated below in Schemes 16-26.

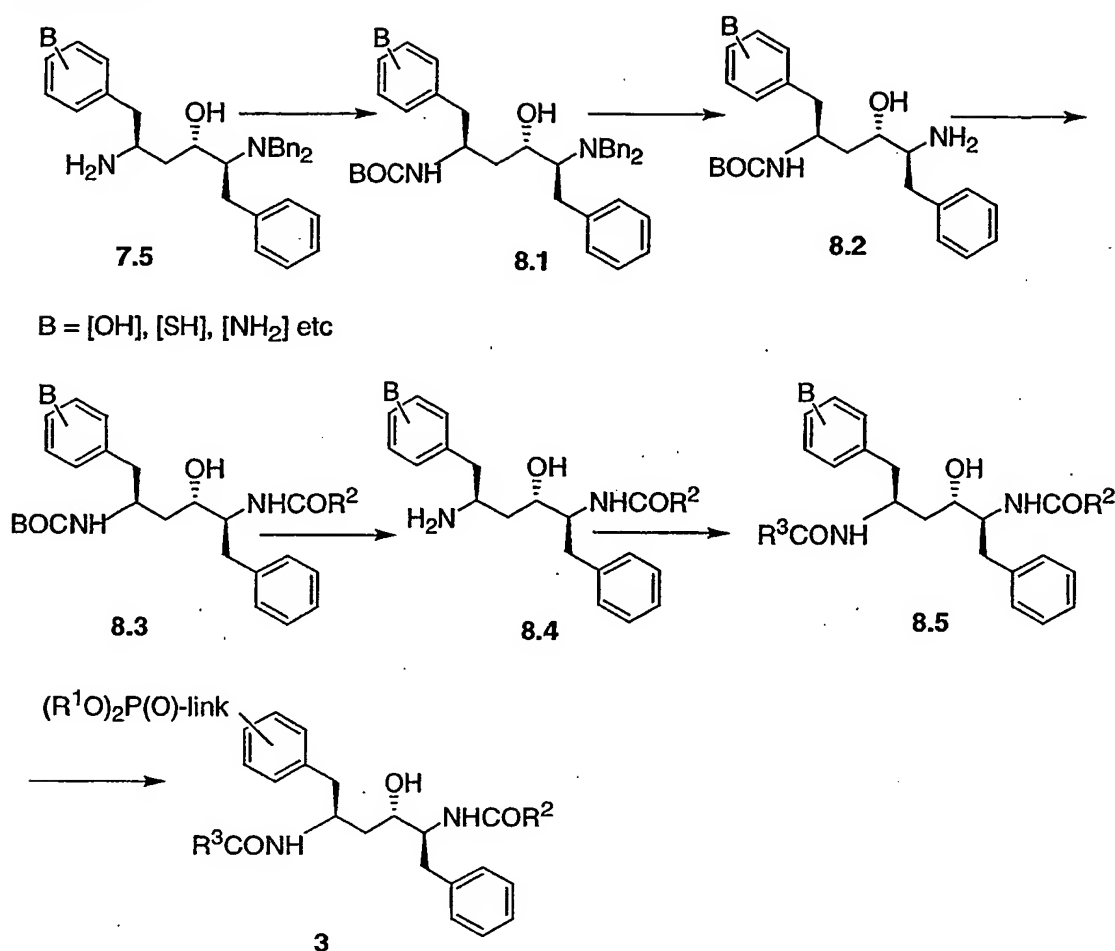
Scheme 6



Scheme 7



Scheme 8



Preparation of the phosphonate intermediates 4.

5

Scheme 9 illustrates the preparation of the intermediate phosphonate esters 9.2 in which the substituent A, which is the phosphonate ester moiety or a precursor group thereto, is attached to one of the urea nitrogen atoms in the carboxylic acid reactant 9.1. The preparation of the carboxylic acid reactant 9.1 is described below, Schemes 24-25. In this procedure, the amine 1.4, prepared as described in Scheme 1, is reacted with the carboxylic acid 9.1, to afford the amide 9.2. The reaction between the amine 1.4 and the carboxylic acid 9.1, or an activated derivative thereof, is conducted under the same general conditions as those described above for the preparation of the amide 1.6 (Scheme 1). Preferably, the reactants are combined in the

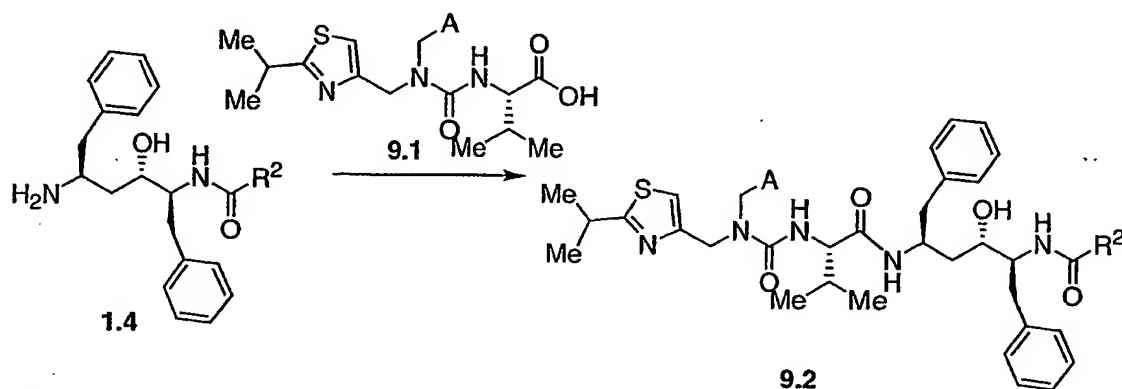
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presence of hydroxybenztriazole and a carbodiimide, as described in U.S. Patent 5,484,801, to yield the amide product **9.2**.

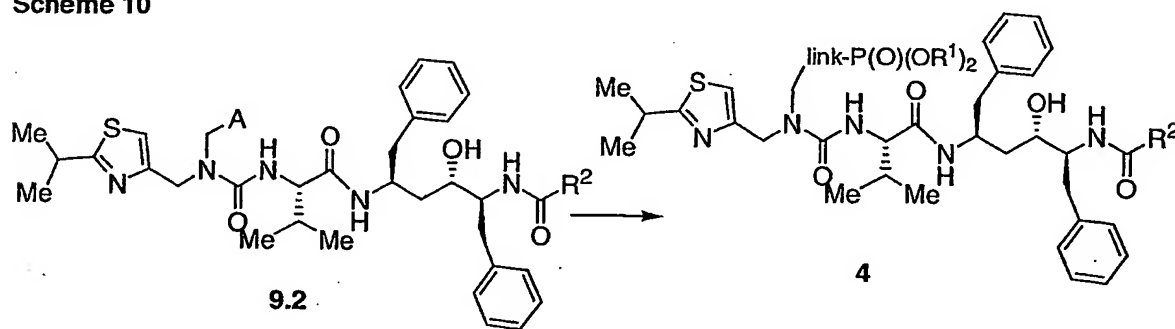
The procedure shown in Scheme 9 describes the preparation of the compounds **9.2** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor group thereto, such as

- 5 [OH], [SH], [NH], as described below. Scheme 10 depicts the conversion of compounds **9.2** in which A is [OH], [SH], [NH], into the compounds **4**, in which the group A has been transformed into the group link-P(O)(OR¹)₂. The methods for accomplishing this transformation are described below, Schemes 16-26.

Scheme 9



Scheme 10



Preparation of the phosphonate intermediates 5.

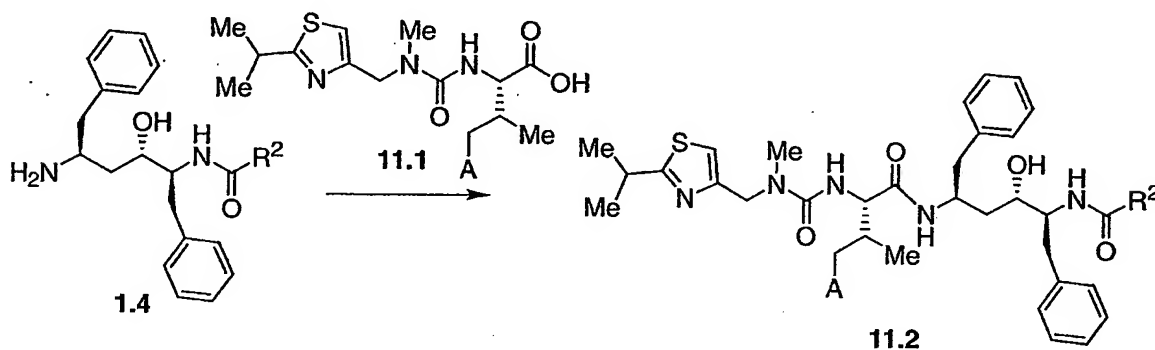
- 15 Scheme 11 illustrates the preparation of the intermediate phosphonate esters **11.2** in which the substituent A, which is the phosphonate ester moiety or a precursor group thereto, is attached to the valine moiety in the carboxylic acid reactant **11.1**. The preparation of the carboxylic acid reactant **11.1** is described below, Scheme 26. The reaction between the amine **1.4** and the

carboxylic acid **11.1**, or an activated derivative thereof, is conducted under the same general conditions as those described above for the preparation of the amide **1.3** (Scheme 1).

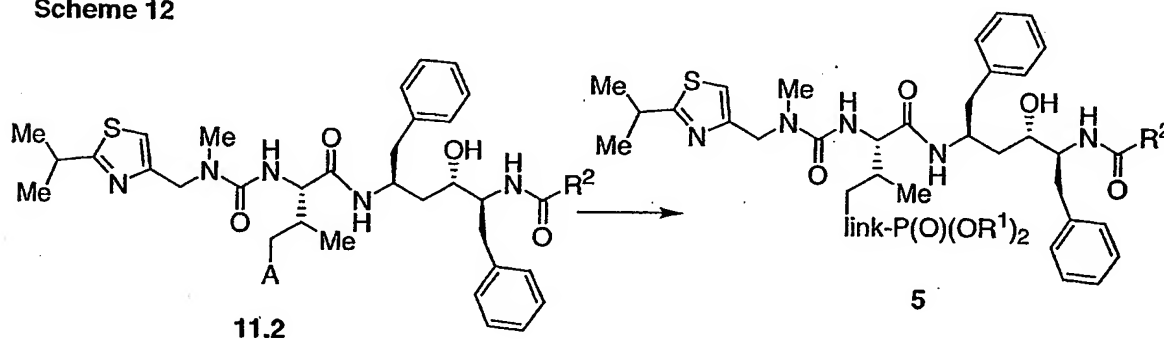
Preferably, the reactants are combined in the presence of hydroxybenztriazole and a carbodiimide, as described in U.S. Patent 5,484,801, to yield the amide product **11.2**.

- 5 The procedure shown in Scheme 11 describes the preparation of the compounds **11.2** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor group thereto, such as [OH], [SH], [NH] Ha, as described below. Scheme 12 depicts the conversion of compounds **11.2** in which A is [OH], [SH], [NH] Br, into the compounds **5**, in which the group A has been transformed into the group link-P(O)(OR¹)₂. The methods for accomplishing this
- 10 transformation are described below, Schemes 16-26.

Scheme 11



Scheme 12



Preparation of carboxylic acids 1.5, with a phosphonate moiety attached to the isopropyl group.

5 Scheme 13 illustrates the preparation of carboxylic acid reactants 1.5, in which a substituent A, attached to the isopropyl group, is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor group thereto, such as [OH], [SH], [NH] Br. During the series of reaction shown in Scheme 13, the group A may, at an appropriate stage, be converted into the group $\text{link-P(O)(OR}^1\text{)}_2$, according to the knowledge of one skilled in the art. Alternatively, the carboxylic acid 1.5, in which A is
10 $\text{link-P(O)(OR}^1\text{)}_2$, may be incorporated into the diamide compounds 1.6, as described above, (Schemes 1 and 2) before effecting the transformation of the group A into the group $\text{link-P(O)(OR}^1\text{)}_2$.

As shown in Scheme 13, a substituted derivative of isobutyramide 13.1 is converted into the corresponding thioamide 13.2. The conversion of amides into thioamides is described in
15 Synthetic Organic Chemistry, by R. B. Wagner and H. D. Zook, Wiley, 1953, p. 827. The amide is reacted with a sulfur-containing reagent such as phosphorus pentasulfide or Lawesson's reagent, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Wiley, Vol. 13, p. 38, to yield the thioamide 13.2. Preferably, the amide 13.1 is reacted with phosphorus pentasulfide in ether solution, at ambient temperature, as described in
20 U.S. Patent 5,484,801, to afford the amide 13.2. The latter compound is then reacted with 1,3-dichloroacetone 13.3 to produce the substituted thiazole 13.4. The preparation of thiazoles by the reaction between a thioamide and a chloroketone is described, for example, in Heterocyclic Chemistry, by T. A. Gilchrist, Longman, 1997, p. 321. Preferably, equimolar amounts of the reactants are combined in acetone solution at reflux temperature, in the
25 presence of magnesium sulfate, as described in U.S. Patent 5,484,801, to produce the thiazole product 13.4. The chloromethyl thiazole 13.4 is then reacted with methylamine to afford the substituted methylamine 13.6. The preparation of amines by the reaction of amines with alkyl halides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397. Typically, the components are reacted together in a polar solvent
30 such as an alkanol or dimethylformamide and the like. Preferably, the chloro compound 13.4 is reacted with excess aqueous methylamine at ambient temperature, as described in U.S. Patent 5,484,801, to afford the amine product 13.6. The amine is then converted into the urea

derivative **13.8** by reaction with an activated derivative of the valine carbamic acid **13.7**, in which X is a leaving group such as alkanoyloxy or 4-nitrophenoxy. The preparation of ureas by the reaction between carbamic acid derivatives and amines is described in Chem. Rev., 57, 47, 1957. Suitable carbamic acid derivatives are prepared by the reaction between an amine and an alkyl or aryl chloroformate, for example as described in WO 9312326. Preferably, the reaction is performed using carbamic acid derivative **13.7**, in which X is 4-nitrophenoxy, and the amine **13.8**; the reaction is conducted at about 0°C in an inert solvent such as dichloromethane, in the presence of an organic base such as dimethylaminopyridine or N-methylmorpholine, as described in U.S. Patent 5,484,801, to yield the urea product **13.8**. The ester group present in the urea product **13.8** is then hydrolyzed to afford the corresponding carboxylic acid **1.5**. Hydrolysis methods for converting esters into carboxylic acids are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 981. The methods include the use of enzymes such as pig liver esterase, and chemical methods such as the use of alkali metal hydroxides in aqueous organic solvent mixtures. Preferably, the methyl ester is hydrolyzed by treatment with lithium hydroxide in aqueous dioxan, as described in U.S. Patent 5,848,801, to yield the carboxylic acid **1.5**.

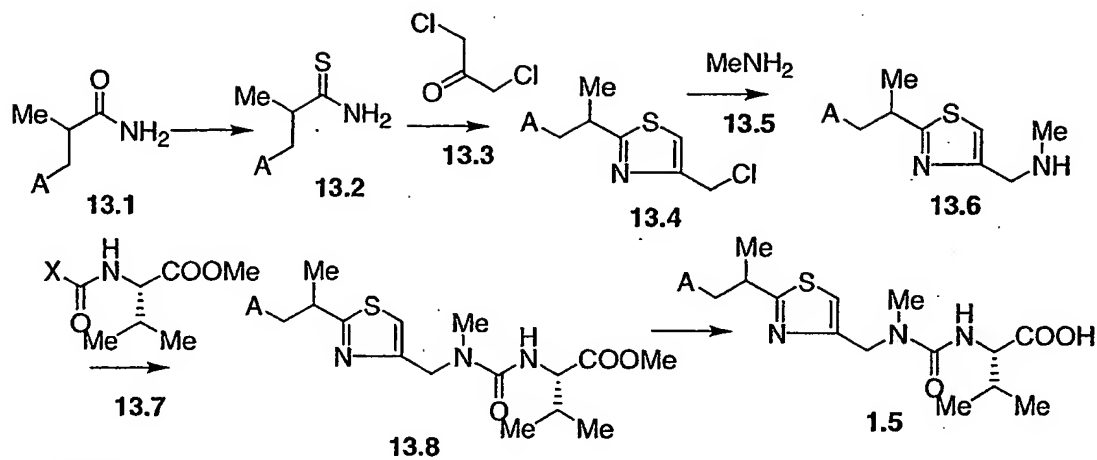
Scheme **14** illustrates the preparation of the carboxylic acids **9.1** in which the group A, attached to the amine moiety, is either the group link-P(O)(OR¹)₂ or a precursor group thereto, such as [OH], [SH], [NH] Br. During the series of reaction shown in Scheme **14**, the group A may, at an appropriate stage, be converted into the group link-P(O)(OR¹)₂, according to the knowledge of one skilled in the art. Alternatively, the carboxylic acid **9.1**, in which A is link-P(O)(OR¹)₂, may be incorporated into the diamide compounds **9.2**, as described above, (Scheme **9**) before effecting the transformation of the group A into the group link-P(O)(OR¹)₂.

As shown in Scheme **14**, 4-chloromethyl-2-isopropyl-thiazole **14.1**, prepared as described in WO 9414436, is reacted with an amine **14.2**, in which A is as described above, to afford the amine **13.6**. The conditions for the alkylation reaction are the same as those described above for the preparation of the amine **13.6**. The product is then transformed, via the intermediate ester **14.4**, into the carboxylic acid **9.1**. The conditions for the reactions required to transform the amine **14.3** into the carboxylic acid **9.1** are the same as those described above (Scheme **13**) for the analogous chemical steps.

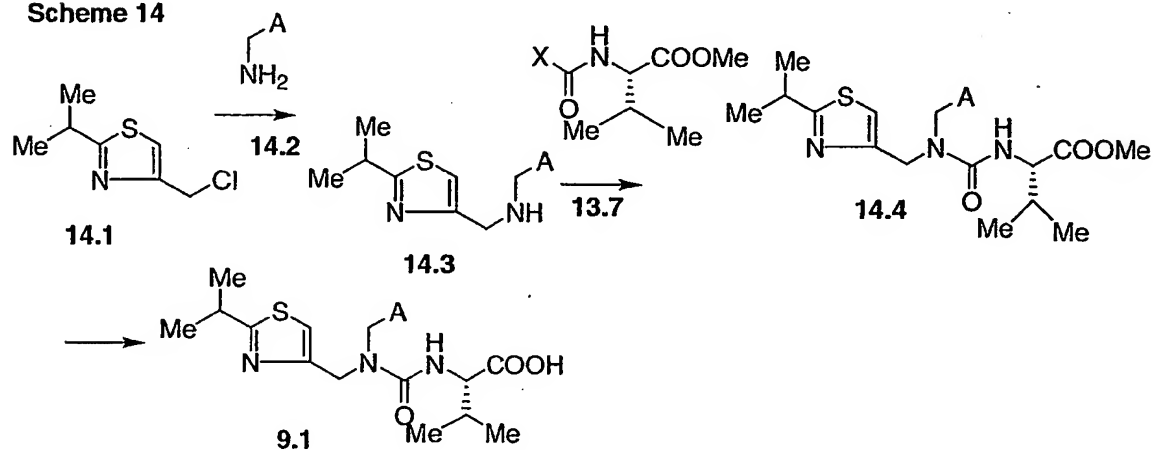
Scheme 15 illustrates the preparation of the carboxylic acids **11.1** in which the group A, attached to the valine moiety, is either the group link-P(O)(OR¹)₂ or a precursor group thereto, such as [OH], [SH], [NH] Br. During the series of reaction shown in Scheme 15, the group A may, at an appropriate stage, be converted into the group link-P(O)(OR¹)₂, according to the knowledge of one skilled in the art. Alternatively, the carboxylic acid **11.1**, in which A is link-P(O)(OR¹)₂ may be incorporated into the diamide compounds **11.2**, as described above, (Scheme 11) before effecting the transformation of the group A into the group link-P(O)(OR¹)₂.

As shown in Scheme 15, (2-isopropyl-thiazol-4-ylmethyl)-methyl-amine, **15.1**, prepared as described in WO 9414436, is reacted with a substituted valine derivative **15.2**, in which the group A is as defined above. Methods for the preparation of the valine derivatives **15.2** are described below, Scheme 26. The resultant ester **15.3** is then hydrolyzed, as described above, to afford the carboxylic acid **11.1**

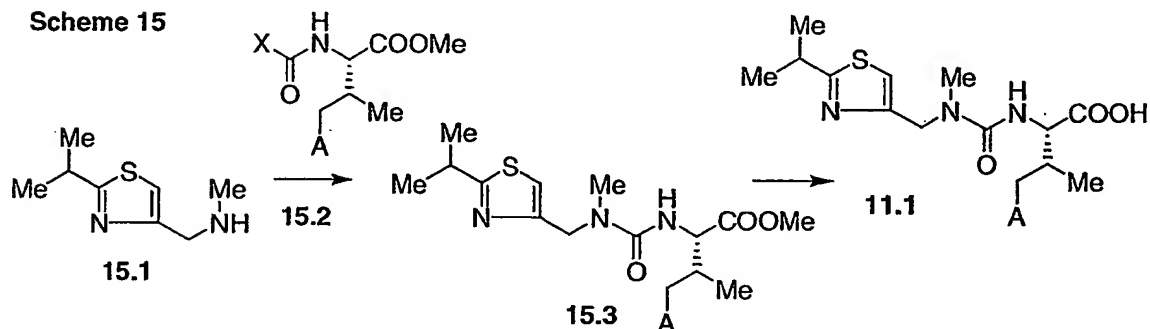
Scheme 13



Scheme 14



Scheme 15



Preparation of phenylalanine derivatives 4.1 incorporating phosphonate moieties.

Scheme 16 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives 16.1.

In this procedure, a hydroxy or mercapto-substituted phenylalanine is converted into the benzyl ester 16.2. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester 16.2 is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p 277. For example, suitable protecting groups for phenols and thiophenols include tert-butyldimethylsilyl or tert-butyldiphenylsilyl. Thiophenols may also be protected as S-adamantyl groups, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. The protected hydroxy- or mercapto ester 16.3 is then reacted with a benzyl or substituted benzyl halide and a base, for example as described in U.S. Patent 5,491,253, to afford the N, N-dibenzyl product 16.4. For example, the amine 16.3 is reacted at ca. 90°C with two molar equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, to afford the tribenzylated product 16.4, as described in U.S. Patent 5,491,253. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride and the like, in a solvent such as tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl groups can be removed by treatment with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.

The resultant phenol or thiophenol **16.5** is then reacted under various conditions to provide protected phenylalanine derivatives **16.9**, **16.10** or **16.11**, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

In this step, the phenol or thiophenol **16.5** is reacted with a dialkyl bromoalkyl phosphonate **16.6** to afford the product **16.9**. The alkylation reaction between **16.5** and **16.6** is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate. The reaction is performed at from ambient temperature to ca. 80°C, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product **16.9**.

- 10 For example, as illustrated in Scheme 16, Example 1, a hydroxy-substituted phenylalanine derivative such as tyrosine, **16.12** is converted, as described above, into the benzyl ester **16.13**. The latter compound is then reacted with one molar equivalent of chloro tert-butyltrimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether **16.14**. This compound is then converted, as
- 15 described above, into the tribenzylated derivative **16.15**. The silyl protecting group is removed by treatment of **16.15** with a tetrahydrofuran solution of tetrabutyl ammonium fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol **16.16**. The latter compound is then reacted in dimethylformamide at ca. 60°C, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **16.17** (Aldrich), in the presence
- 20 of cesium carbonate, to afford the alkylated product **16.18**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **16.12**, different hydroxy or thio-substituted phenylalanine derivatives **16.1**, and/or different bromoalkyl phosphonates **16.6**, the corresponding ether or thioether products **16.9** are obtained.

- 25 Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **16.5** is reacted with a dialkyl hydroxymethyl phosphonate **16.7** under the conditions of the Mitsunobu reaction, to afford the ether or thioether compounds **16.10**. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in
- 30 Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an

aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products 16.10.

For example, as shown in Scheme 16, Example 2, 3-mercaptophenylalanine 16.19, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester 16.20. The

5 resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether 16.21. This compound is then converted, as described above for the preparation of the compound 16.4, into the tribenzyl derivative 16.22. The 4-methoxybenzyl group is then removed by the reaction of the

10 thioether 16.22 with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in J.Org. Chem., 52, 4420, 1987, to afford the thiol 16.23. The latter compound is reacted, under the conditions of the Mitsunobu reaction, with diethyl hydroxymethyl phosphonate 16.7, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product 16.24.

15 Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative 16.19, different hydroxy or mercapto-substituted phenylalanines 16.1, and/or different dialkylhydroxymethyl phosphonates 16.7, the corresponding products 16.10 are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative 16.5

20 is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate 16.8 in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products 16.11.

For example, as illustrated in Scheme 16, Example 3, 3-hydroxyphenylalanine 16.25 (Fluka) is

25 converted, using the procedures described above, into the tribenzylated compound 16.26. The latter compound is reacted, in dimethylformamide at ca. 50°C, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate 16.27, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product 16.28.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine

30 derivative 16.25, different hydroxy or mercapto-substituted phenylalanines 16.1, and/or different dialkyl trifluoromethanesulfonyloxymethylphosphonates 16.8, the corresponding products 16.11 are obtained.

Scheme 17 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a
5 formyl-substituted tribenzylated phenylalanine derivative 17.3 and a dialkyl aminoalkylphosphonate 17.4.

In this procedure, a hydroxymethyl-substituted phenylalanine 17.1 is converted into the tribenzylated derivative 17.2 by reaction with three equivalents of a benzyl halide, for example, benzyl chloride, in the presence of an organic or inorganic base such as diazabicyclononene or
10 potassium carbonate. The reaction is conducted in a polar solvent optionally in the additional presence of water. For example, the aminoacid 17.1 is reacted with three equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, as described in U.S. Patent 5,491,253, to afford the product 17.2. The latter compound is then oxidized to afford the corresponding aldehyde 17.3. The conversion of alcohols to aldehydes is described, for
15 example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product 17.3. For example, the carbinol 17.2 is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in J. Org. Chem., 43, 2480, 1978, to yield the aldehyde 17.3. This compound is
20 reacted with a dialkyl aminoalkylphosphonate 17.4 in the presence of a suitable reducing agent to afford the amine product 17.5. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or
25 ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. For example, 3-(hydroxymethyl)-phenylalanine 17.6, prepared as described in Acta Chem.
30 Scand. Ser. B, 1977, B31, 109, is converted, as described above, into the formylated derivative 17.7. This compound is then reacted with a dialkyl aminoethylphosphonate 17.8,

prepared as described in J. Org. Chem., 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product 17.9.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine 17.6, different hydroxymethyl phenylalanines 17.1, and/or different aminoalkyl phosphonates 17.4, the corresponding products 17.5 are obtained.

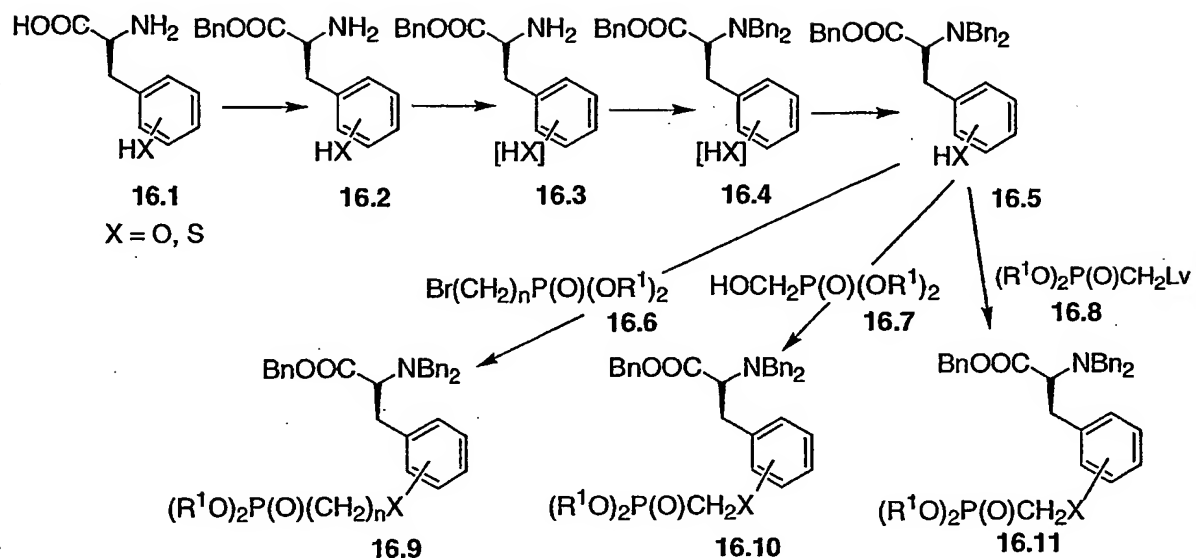
Scheme 18 depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine 18.1 is converted, as described above, (Scheme 17) into the tribenzylated derivative 18.2. The product is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite 18.3 to produce the phosphonate ester 18.4. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.

For example, 3-bromophenylalanine 18.5, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme 17) into the tribenzylated compound 18.6. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite 18.7, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 18.8.

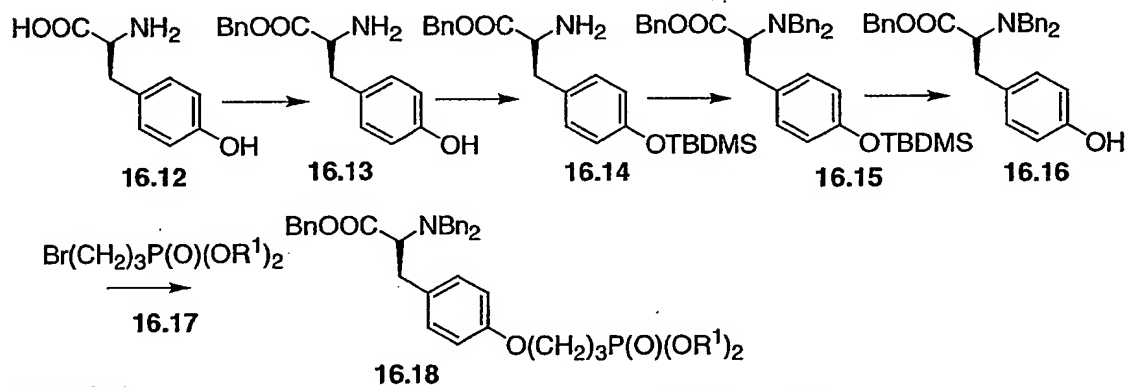
Using the above procedures, but employing, in place of 3-bromophenylalanine 18.5, different bromophenylalanines 18.1, and/or different dialkylphosphites 18.3, the corresponding products 18.4 are obtained.

Scheme 16

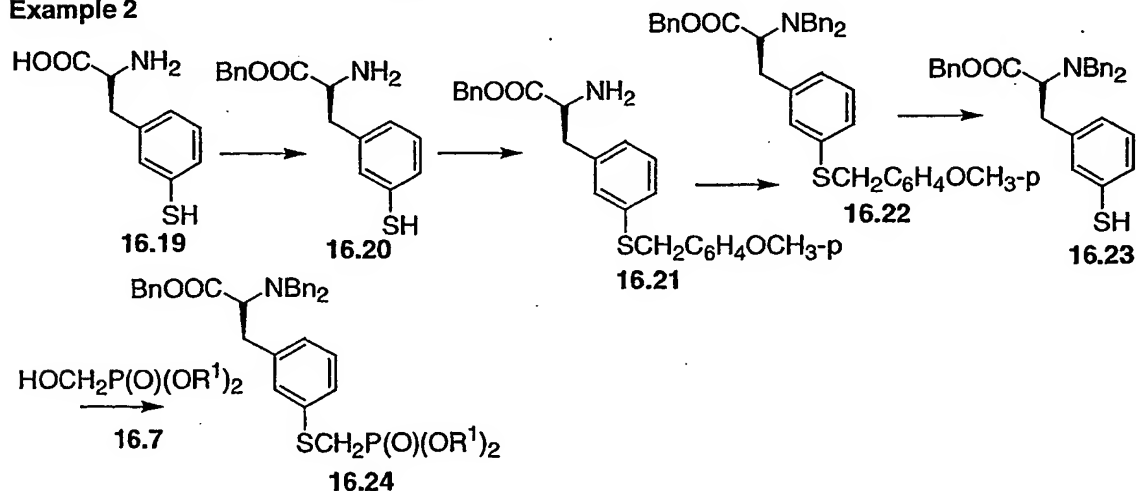
Method



Example 1

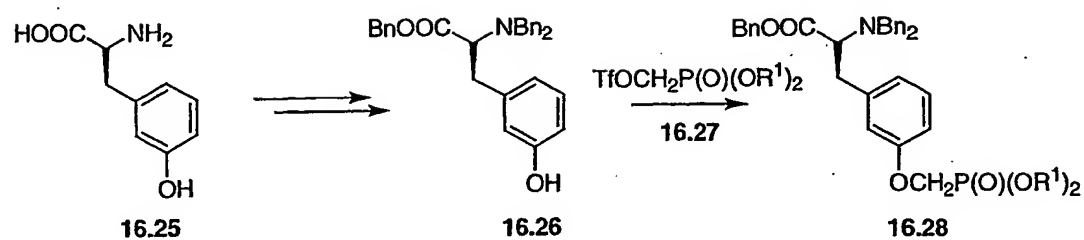


Example 2



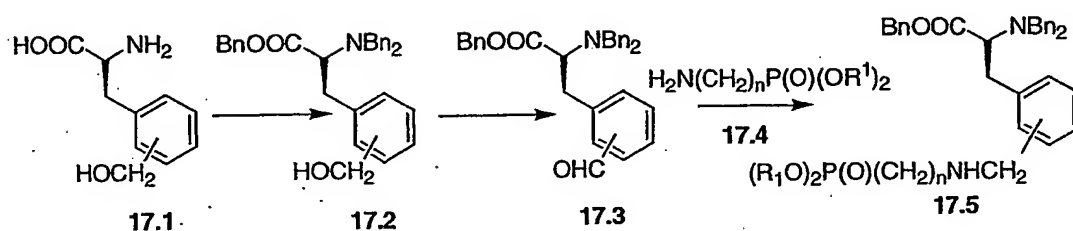
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Example 3

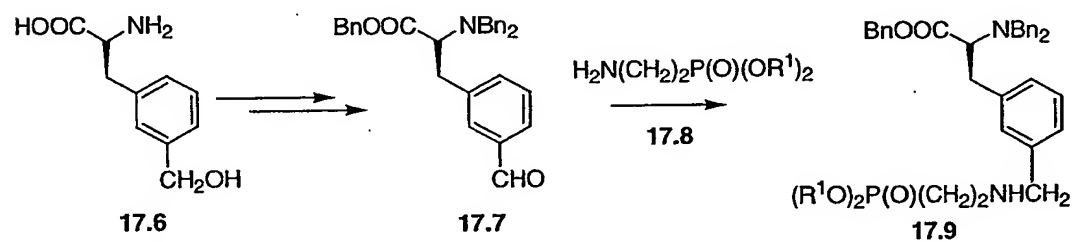


Scheme 17

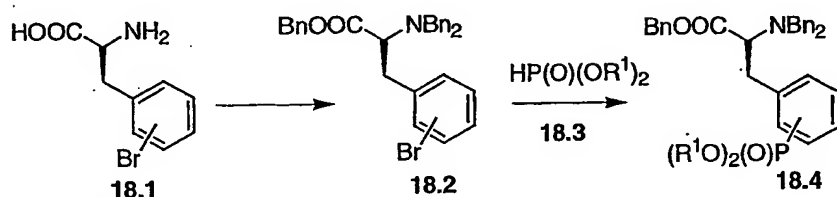
Method



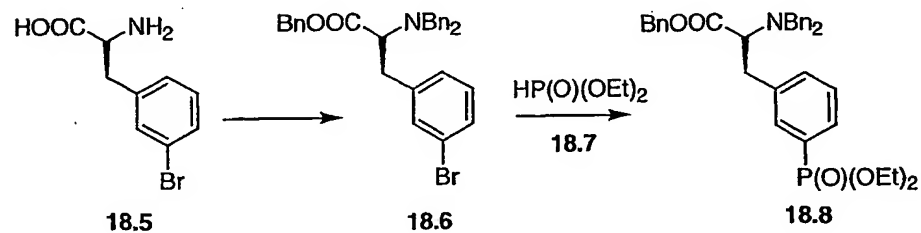
Example



Scheme 18



Example



Preparation of phosphonate esters with structure 3.

Scheme 19 illustrates the preparation of compounds 3 in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, the ketonitrile 7.1, prepared as described in J. Org. Chem., 1994, 59, 4080, is reacted with a bromobenzylmagnesium halide reagent 19.1. The resultant ketoenamine 19.2 is then converted into the diacylated bromophenyl carbinol 19.3. The conditions required for the conversion of the ketoenamine 19.2 into the carbinol 19.3 are similar to those described above (Scheme 4) for the conversion of the ketoenamine 4.5 into the carbinol 4.12. The product 19.3 is then reacted with a dialkyl phosphite 18.3, in the presence of a palladium (0) catalyst, to yield the phosphonate ester 19.4. The conditions for the coupling reaction are the same as those described above (Scheme 18) for the preparation of the phosphonate ester 18.4.

For example, the ketonitrile 7.1 is reacted, in tetrahydrofuran solution at -40°C, with three molar equivalents of 4-bromobenzylmagnesium bromide 19.5, the preparation of which is described in Tetrahedron, 2000, 56, 10067, to afford the ketoenamine 19.6. The latter compound is then converted into the bromophenyl carbinol 19.7, using the sequence of reactions described above (Scheme 4) for the conversion of the ketoenamine 4.5 into the carbinol 4.12. The resultant bromo compound 19.7 is then reacted with diethyl phosphite 18.3 and triethylamine, in toluene solution at reflux, in the presence of tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 19.8.

Using the above procedures, but employing, in place of 4-bromobenzylmagnesium bromide 19.5, different bromobenzylmagnesium halides 19.1 and/or different dialkyl phosphites 18.3, there are obtained the corresponding phosphonate esters 19.4.

Scheme 20 illustrates the preparation of compounds 3 in which the phosphonate ester moiety is attached to the nucleus by means of a phenyl ring. In this procedure, a bromophenyl-substituted benzylmagnesium bromide 20.1, prepared from the corresponding bromomethyl compound by reaction with magnesium, is reacted with the ketonitrile 7.1. The conditions for this transformation are the same as those described above (Scheme 4). The product of the Grignard addition reaction is then transformed, using the sequence of reactions described

above, (Scheme 4) into the diacylated carbinol 20.2. The latter compound is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite 18.3, to afford the phenylphosphonate 20.3. The procedure for the coupling reaction is the same as those described above for the preparation of the phosphonate 19.8.

- 5 For example, 4-(4-bromophenyl)benzyl bromide, prepared as described in DE 2262340, is reacted with magnesium to afford 4-(4-bromophenyl)benzylmagnesium bromide 20.4. This product is then reacted with the ketonitrile 7.1, as described above, to yield, after the sequence of reactions shown in Scheme 4, the diacylated carbinol 20.5. The latter compounds then reacted, as described above, (Scheme 18) with a dialkyl phosphite 18.3, to afford the
10 phenylphosphonate 20.6.

Using the above procedures, but employing, in place of 4-(4-bromophenyl)benzyl bromide 20.4, different bromophenylbenzyl bromides 20.1, and/or different dialkyl phosphites 18.3, the corresponding products 20.3 are obtained.

- 15 Scheme 21 depicts the preparation of phosphonate esters 3 in which the phosphonate group is attached by means of a heteroatom and a methylene group. In this procedure, a hetero-substituted benzyl alcohol 21.1 is protected, affording the derivative 21.2. The protection of phenyl hydroxyl, thiol and amino groups are described, respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10,
20 p. 277, 309. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, as
25 described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. Amino groups can be protected, for example by dibenzylation. The conversion of amines into dibenzylamines, for example by treatment with benzyl bromide in a polar solvent such as acetonitrile or aqueous ethanol, in the presence of a base such as triethylamine or sodium carbonate, is described in Protective Groups in Organic Synthesis, by
30 T.W. Greene and P.G. M Wuts, Wiley, Second Edition 1990, p. 364. The resultant protected benzyl alcohol 21.1 is converted into a halo derivative 21.2, in which Ha is chloro or bromo. The conversion of alcohols into chlorides and bromides is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. For example, benzyl alcohols **21.2** can be transformed into the chloro compounds **21.3**, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols can be transformed into

5 bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. The resultant protected benzyl halide **21.3** is then converted into the corresponding benzylmagnesium halide **21.4** by reaction with magnesium metal in an ethereal solvent, or by a Grignard exchange reaction treatment with an alkyl magnesium halide. The resultant substituted benzylmagnesium halide **21.4** is then converted,

10 using the sequence of reactions described above (Scheme 4) for the preparation of the diacylated carbinol **4.11**, into the carbinol **21.5** in which the substituent XH is suitably protected.

The protecting group is then removed to afford the phenol, thiophenol or amine **21.6**. Deprotection of phenols, thiophenols and amines is described respectively in Protective

15 Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am. Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the

20 corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978. N,N-dibenzyl amines can be converted into the unprotected amines by catalytic reduction in the presence of a palladium catalyst, as described above (Scheme 1). The resultant phenol, thiophenol or

amine **21.6** is then converted into the phosphonate ester **21.7** by reaction with an activated derivative of a dialkyl hydroxymethyl phosphonate **16.27**, in which Lv is a leaving group. The

25 reaction is conducted under the same conditions as described above for the conversion of **16.5** to **16.11** (Scheme 16).

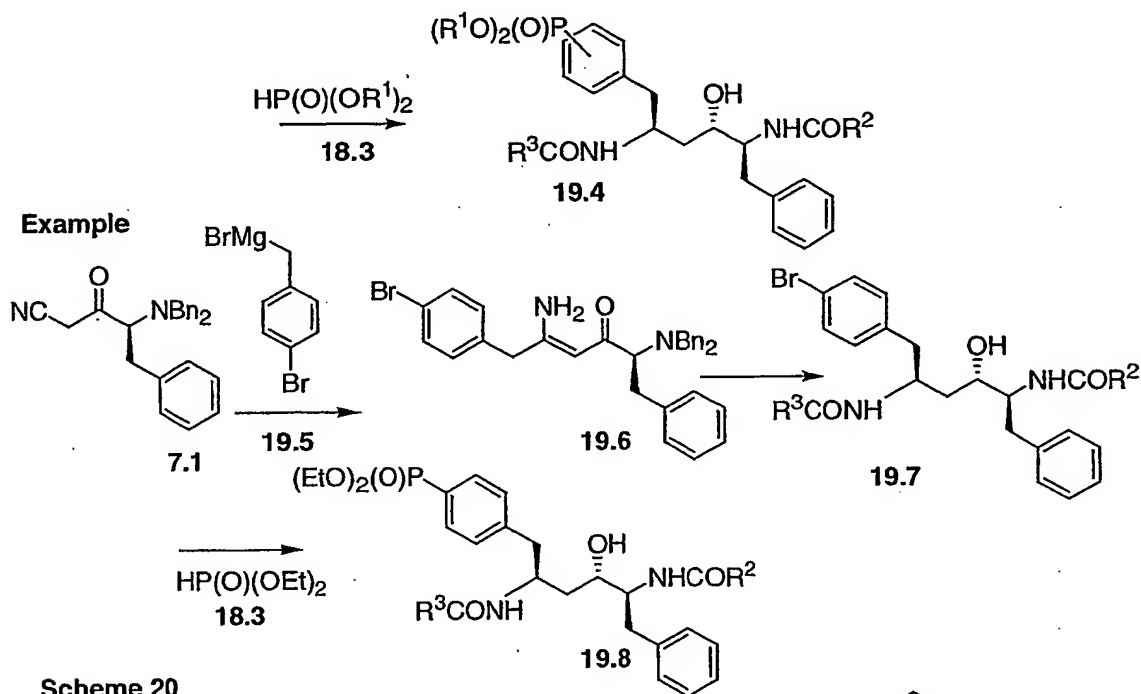
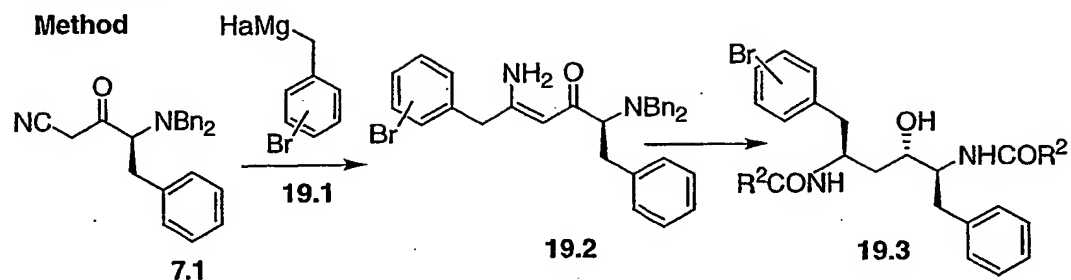
For example, 3-hydroxybenzyl alcohol **21.8** (Aldrich) is reacted with chlorotriisopropylsilane and imidazole in dimethylformamide, as described in Tet. Lett., 2865, 1964, to afford the silyl ether **21.9**. This compound is reacted with carbon tetrabromide and triphenylphosphine in

30 dichloromethane, as described in J. Am. Chem. Soc., 109, 2738, 1987, to afford the brominated product **21.10**. This material is reacted with magnesium in ether to afford the Grignard reagent **21.11**, which is then subjected to the series of reaction shown in Scheme 4 to

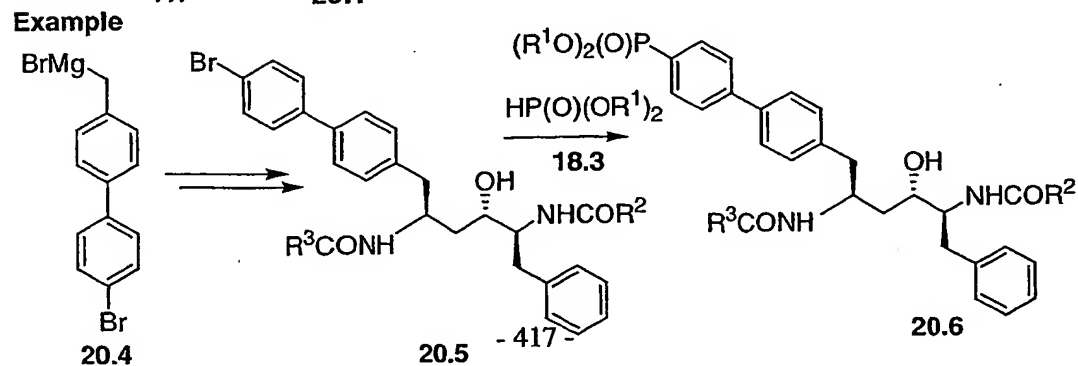
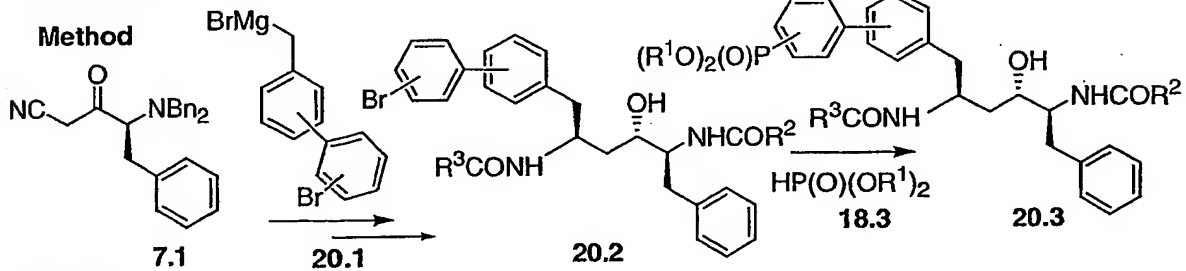
afford the carbinol **21.12**. The triisopropylsilyl protecting group is then removed by treatment of the ether **21.12** with tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Org. Chem., 51, 4941, 1986. The resultant phenol **21.13** is then reacted with a dialkyl trifluoromethanesulfonyloxymethylphosphonate **16.27**, prepared as described in Tet. Lett., 1986, 27, 1477, in dimethylformamide solution at 60°C in the presence of cesium carbonate, to afford the phosphonate product **21.14**.

Using the above procedures, but employing, in place of 3-hydroxybenzyl alcohol **21.8**, different hydroxy, mercapto or amino-substituted benzyl alcohols **21.1**, and/or different dialkyl trifluoromethanesulfonyloxymethyl phosphonates **16.27**, the corresponding products **21.7** are obtained.

Scheme 19

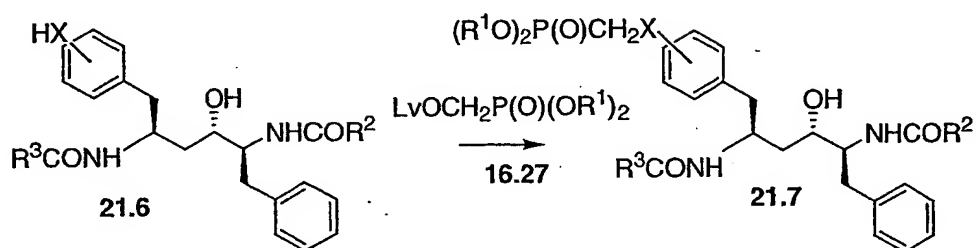
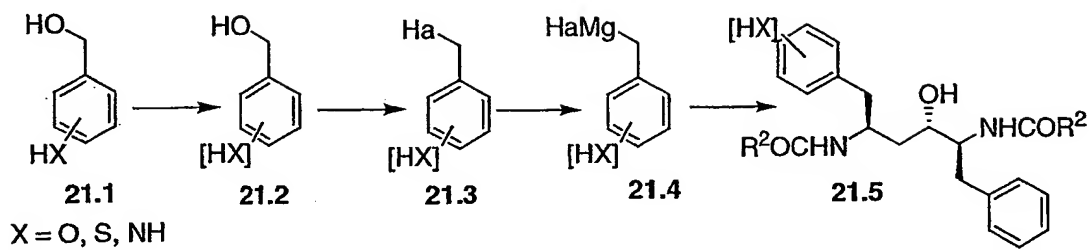


Scheme 20

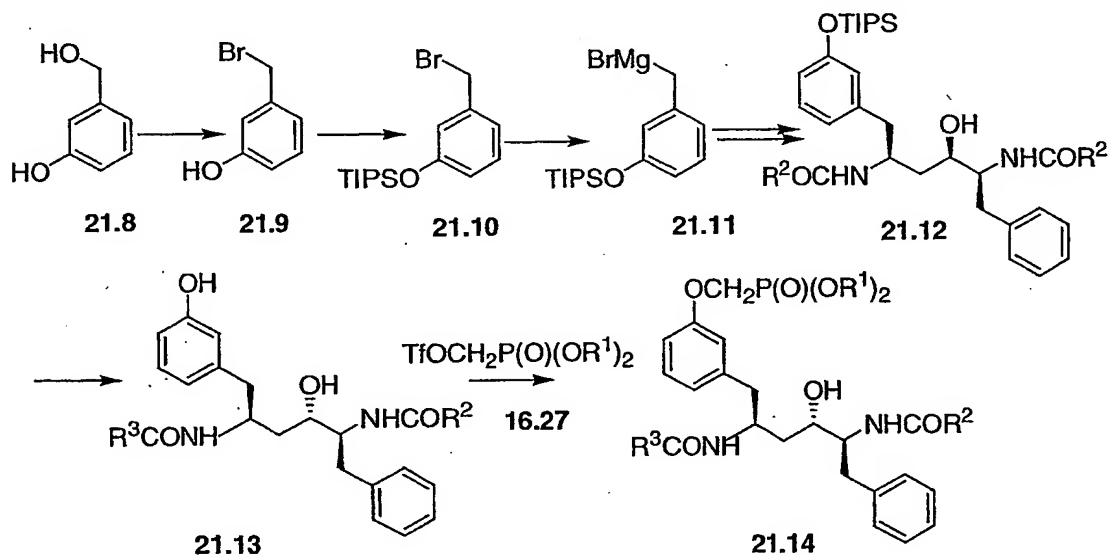


Scheme 21

Method



Example



Preparation of phosphonate-containing carboxylic acids 1.5.

Scheme 22 illustrates methods for the preparation of carboxylic acids 1.5, in which A is Br, and methods for the conversion of the bromo substituent into various phosphonate-containing substituents.

In this procedure, 3-bromo-2-methylpropanamide 22.1 is substituted for the isobutyramide derivative 13.1 in the reaction sequence illustrated in Scheme 13, so as to afford 2-{3-[2-(2-bromo-1-methyl-ethyl)-thiazol-4-ylmethyl]-3-methyl-ureido}-3-methyl-butyric acid methyl ester, 22.2. The conditions required for the various reactions are the same as those described above (Scheme 13). The bromo-substituted ester 22.2 is then subjected to various transformations so as to introduce phosphonate-containing substituents. For example, the ester 22.2 is reacted with a trialkyl phosphate 22.3 in an Arbuzov reaction, to afford the phosphonate ester 22.4. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992, 115. The reaction is performed by heating the substrate at 100°C to 150°C with an excess of the trialkyl phosphite. The methyl ester group in the phosphonate product 22.4 is then hydrolyzed, using the procedures described above, (Scheme 13) to prepare the carboxylic acid 22.5.

For example, as shown in Scheme 22, Example 1, the bromo compound 22.2 is heated at 120°C with a ten molar excess of tribenzyl phosphite 22.6 to afford the benzylphosphonate 22.7. Hydrolysis of the methyl ester, as described above, then yields 2-(3-{2-[2-(bis-benzyloxy-phosphoryl)-1-methyl-ethyl]-thiazol-4-ylmethyl}-3-methyl-ureido)-3-methyl-butyric acid 22.8.

Alternatively, the bromoester 22.2 is oxidized to the corresponding aldehyde 22.9. Methods for the oxidation of bromo compounds to the corresponding aldehyde are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989 p. 599. The transformation can be effected by reaction of the aldehyde with dimethyl sulfoxide, optionally in the presence of a silver salt, as described in Chem. Rev., 67, 247, 1967. Alternatively, the bromo compound is reacted with trimethylamine oxide, as described in Ber., 94, 1360, 1961, to prepare 3-methyl-2-{3-methyl-3-[2-(1-methyl-2-oxo-ethyl)-thiazol-4-ylmethyl]-ureido}-butyric-acid methyl ester 22.9. The aldehyde is then reacted with a dialkyl aminoalkyl phosphonate 22.10 in a reductive amination reaction to afford the

aminophosphonate 22.11. The conditions for the reductive amination reaction are the same as those described above for the preparation of the aminophosphonate 17.5, (Scheme 17). The methyl ester group present in the product 22.11 is then hydrolyzed, as described above, to yield the carboxylic acid 22.12.

- 5 For example, as shown in Scheme 22, Example 2, the bromo compound 22.2 is heated at 80°C in dimethylsulfoxide solution, in the presence of one molar equivalent of silver tetrafluoroborate and triethylamine, as described in J. Chem. Soc., Chem. Comm., 1338, 1970, to afford the aldehyde 22.9. Reductive amination of the product, in the presence of a dialkyl aminoethyl phosphonate 22.13, the preparation of which is described in J. Org. Chem., 2000, 65, 676 and
10 sodium triacetoxy borohydride, then affords the amino phosphonate 22.14. Hydrolysis of the methyl ester, as described above, then afford the carboxylic acid 22.15.

- Alternatively, the bromo compound 22.2 is reacted with a dialkyl thioalkyl phosphonate 22.16 to effect displacement of the bromo substituent to afford the thioether 22.17. The preparation of thioethers by the reaction of bromo compounds with thiols is described, for example, in
15 Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 787. The reactants are combined in the presence of a suitable base, such as sodium hydroxide, dimethylaminopyridine, potassium carbonate and the like, in a polar organic solvent such as dimethylformamide or ethanol, to afford the thioether 22.17. The product is then subjected to hydrolysis, as described above, to afford the carboxylic acid 22.18.

- 20 For example, as shown in Scheme 22, Example 3, the bromo compound 22.2 is reacted with a dialkyl thioethylphosphonate 22.19, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, and dimethylaminopyridine, in dimethylformamide solution at ambient temperature, to yield the thioether 22.20. Hydrolysis of the methyl ester group, as described above, then afford the carboxylic acid 22.21.

25

Scheme 23 illustrates the preparation of carboxylic acids 23.7 in which the phosphonate moiety is attached to the isopropyl group by means of a phenyl ring and a heteroatom. In this procedure, the hydroxy or mercapto substituent on a phenylbutanamide 23.1 is protected. Methods for the protection of hydroxyl and thiol groups are described above (Scheme 21).

- 30 The protected amide 23.2 is then subjected to the series of reactions illustrated in Scheme 13, so as to afford the O- or S-protected ester 23.3. The protecting group is then removed. Methods for the deprotection of phenols and thiophenols are described above (Scheme 16).

The resultant phenol or thiophenol 23.4 is then reacted with a dialkyl bromoalkyl phosphonate 23.5, to afford the ether or thioether compounds 23.6. Conditions for the alkylation of phenols and thiophenols are described above (Scheme 16). The ester groups present in the product 23.6 is then hydrolyzed, as described above, to afford the corresponding carboxylic acid 23.7.

For example, 3-(4-hydroxyphenyl)butyric acid 23.8, prepared as described in J. Med. Chem., 1992, 35, 548, is converted into the acid chloride by reaction with thionyl chloride. The acid chloride is then reacted with excess aqueous ethanolic ammonia to afford the amide 23.9. This compound is converted into the tert. butyldimethylsilyl derivative 23.10 by treatment with tert-butylchlorodimethylsilane and imidazole in dichloromethane. The resultant amide 23.10 is then subjected to the series of reactions shown in Scheme 13, so as to yield the ester 23.11. Desilylation, by treatment with tetrabutylammonium fluoride in tetrahydrofuran, then affords the phenol 23.12. This compound is reacted with a dialkyl bromoethyl phosphonate 23.13 (Aldrich) and potassium carbonate, in dimethylformamide at 80°C, to produce the ether 23.14. Hydrolysis of the ester group, by treatment with aqueous methanolic lithium hydroxide, then affords the carboxylic acid 23.15.

Using the above procedures, but employing, in place of the amide 23.9, different hydroxy- or thio-substituted amides 23.23.1, and/or different bromoalkylphosphonates 23.5, the corresponding products 23.7 are obtained.

20

Scheme 24 and 25 describes the preparation of carboxylic acids 9.1 in which the phosphonate moiety is attached to the amine component. In this procedure, the chloromethylthiazole 14.1, is reacted with a dialkyl aminoalkyl phosphonate 24.1 to produce the substituted amine 24.2. The preparation of amines by reacting amines with alkyl halides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397. Typically, the components are reacted together in a polar solvent such as an alkanol or dimethylformamide and the like, to yield the substituted amine 24.2. The latter compound is then converted into the carboxylic acid 24.3, by means of the series of reactions shown in Scheme 14.

25

For example, the chloromethyl thiazole 14.1 is reacted at 50°C in acetonitrile solution containing potassium carbonate, with one molar equivalent of a dialkyl aminomethyl phosphonate 24.4, prepared as described in Bioorg. Chem., 2001, 29, 77, to afford the

30

substituted amine 24.5. The product is then converted, using the reactions shown in Scheme 14, into the carboxylic acid 24.6.

Using the above procedures, but employing, in place of the dialkyl aminoethyl phosphonate 24.4, different dialkyl aminoalkyl phosphonates 24.1, the corresponding products 24.3 are
5 obtained.

Scheme 25 illustrates the preparation of carboxylic acids 9.1 in which the phosphonate moiety is attached to the amine component by means of a saturated or unsaturated alkyl chain and a phenyl ring. In this procedure, the chloromethylthiazole 14.1 is reacted with allylamine 25.1,
10 using the procedures described above (Scheme 24) to afford allyl-(2-isopropyl-thiazol-4-ylmethyl)-amine 25.2. The ester amine is then converted, by means of the series of reactions shown in Scheme 14, into 2-[3-allyl-3-(2-isopropyl-thiazol-4-ylmethyl)-ureido]-3-methylbutyric acid methyl ester 25.3. This material is coupled with a dialkyl bromo-substituted phenylphosphonate 25.4, under the conditions of the palladium-catalyzed Heck reaction, to
15 afford the coupled product 25.5. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II)
20 acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Hydrolysis of the methyl ester, as described above, then yields the carboxylic acid 25.6. Optionally, the double bond present in the product 25.6 is reduced to afford the dihydro analog 25.7. The double bond is reduced in the presence of a palladium catalyst, such as, for example, 5% palladium on carbon, in a solvent such as methanol or ethanol, to afford the
25 product 25.7.

For example, the allyl-substituted urea 25.3 is reacted with a dialkyl 4-bromophenyl phosphonate 25.8, prepared as described in J. Chem. Soc., Perkin Trans., 1977, 2, 789 in the presence of tetrakis(triphenylphosphine)palladium (0) and triethylamine, to afford the phosphonate ester 25.9. Ester hydrolysis, as described above, then affords the carboxylic acid
30 25.10. Hydrogenation, as described above, then affords the saturated analog 25.11.

Using the above procedures, but employing, in place of the 4-bromophenyl phosphonate 25.8, different bromophenyl phosphonates 25.4, the corresponding products 25.6 and 25.7 are obtained.

- 5 Scheme 26 illustrates the preparation of carboxylic acids 11.1 in which the phosphonate moiety is attached to the valine substructure. In this procedure, 2-amino-4-bromo-3-methylbutyric acid methyl ester 26.1, prepared as described in U.S. Patent 5,346,898, is reacted with a chloroformate, for example 4-nitrophenyl chloroformate, to prepare the activated derivative 26.2 in which X is a leaving group. For example, the aminoester 26.1 is reacted with 4-nitrophenylchloroformate in dichloromethane at 0°C, as described in U.S. 5,484,801, to afford the product 26.2 in which X is 4-nitrophenoxy. The latter compound is reacted with (2-isopropyl-thiazol-4-ylmethyl)-methyl-amine 26.3, prepared as described in U.S. 5,484,801, in the presence of a base such as triethylamine or dimethylaminopyridine, in an inert solvent such as dichloromethane or tetrahydrofuran, to afford 4-bromo-2-[3-(2-isopropyl-thiazol-4-ylmethyl)-3-methyl-ureido]-3-methyl-butyric acid methyl ester 26.4. The bromo compound 26.4 is then oxidized to afford the aldehyde 26.5. The oxidation of bromo compounds to afford the corresponding aldehydes is described above (Scheme 22). In a typical procedure, the bromo compound is heated at 80°C in dimethylsulfoxide solution, optionally in the presence of silver salt such as silver perchlorate or silver tetrafluoroborate, as described in J. Am. Chem. Soc., 81, 4113, 1959, to afford 2-[3-(2-isopropyl-thiazol-4-ylmethyl)-3-methyl-ureido]-3-methyl-4-oxo-butyric acid methyl ester 26.5. The aldehyde is then subjected to a reductive amination procedure, in the presence of a dialkyl aminoalkyl phosphonate 26.6, to afford the amine product 26.7. The preparation of amines by means of reductive alkylation reactions is described above (Scheme 22). Equimolar amounts of the aldehyde 26.5 and the amine 26.6 are reacted in the presence of a boron-containing reducing agent such as, for example, sodium triacetoxyborohydride, to yield the amine 26.7. The methyl ester is then hydrolyzed, as described above, to yield the carboxylic acid 26.8. For example, 2-[3-(2-isopropyl-thiazol-4-ylmethyl)-3-methyl-ureido]-3-methyl-4-oxo-butyric acid methyl ester 26.5 is reacted with a dialkyl aminoethylphosphonate 26.9 and sodium cyanoborohydride, to afford the amine product 26.10. The methyl ester is then hydrolyzed, as described above to yield the carboxylic acid 26.11.

Using the above procedures, but employing, in place of the dialkyl aminoethylphosphonate 26.9, different aminoalkyl phosphonates 26.6, the corresponding products 26.8 are obtained. Alternatively, the bromo-substituted methyl ester 26.4 is then reacted with a dialkyl mercaptoalkyl phosphonate 26.12 to afford the thioether 26.13. The preparation of thioethers

5 by the reaction of bromo compounds with thiols is described, for example, in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 787. The reactants are combined in the presence of a suitable base, such as sodium hydroxide, dimethylamino pyridine, potassium or cesium carbonate and the like, in a polar organic solvent such as dimethylformamide or ethanol, to afford the thioether 26.13. The methyl ester is then

10 hydrolyzed, as described above to yield the carboxylic acid 26.14.

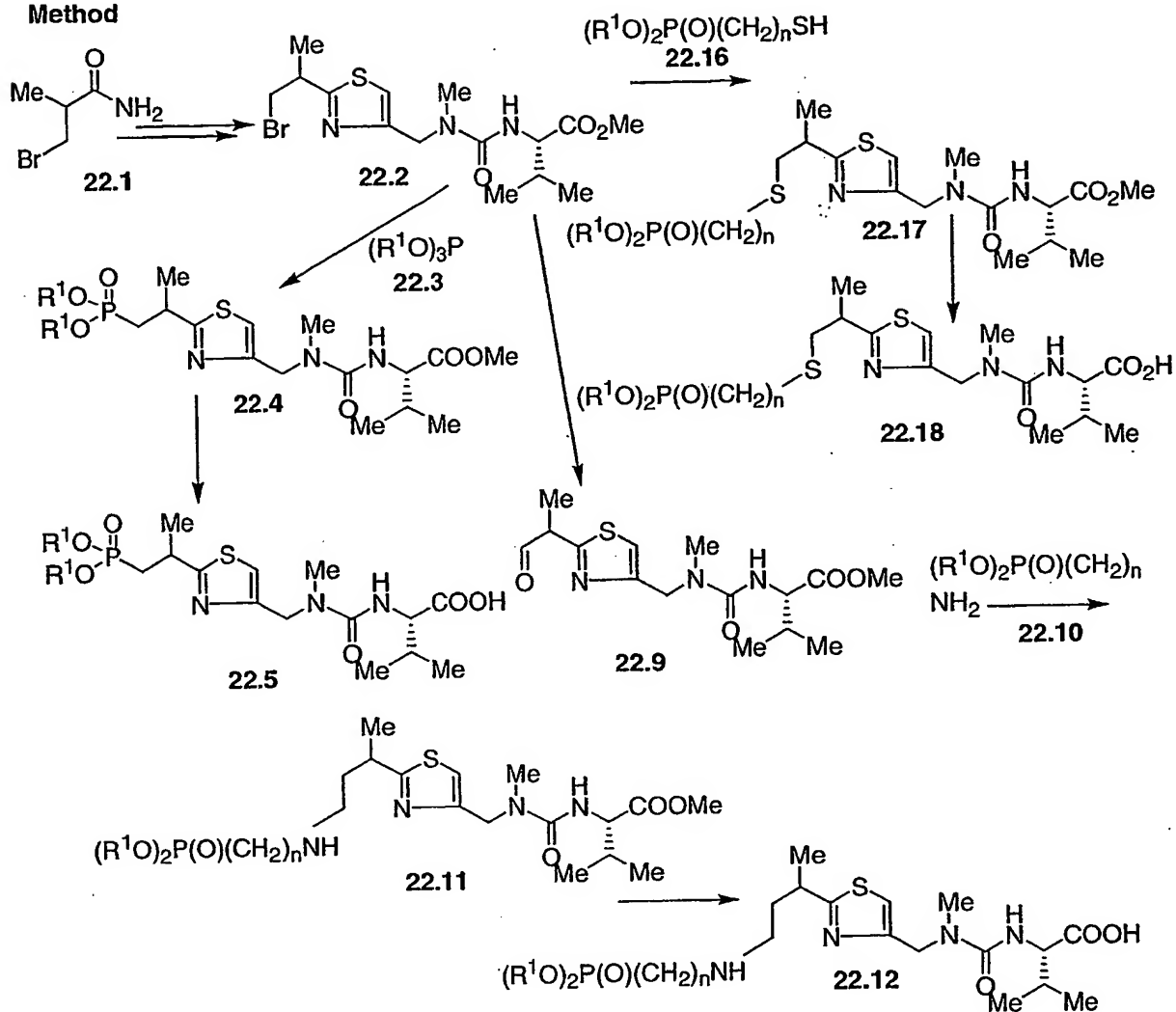
For example, the bromo compound 26.4 is reacted with a dialkyl mercaptoethyl phosphonate 26.15, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, in dimethylformamide solution, in the presence of cesium carbonate, to produce the thio ether product 26.16. The methyl ester is then hydrolyzed, as described above, to yield the

15 carboxylic acid 26.17.

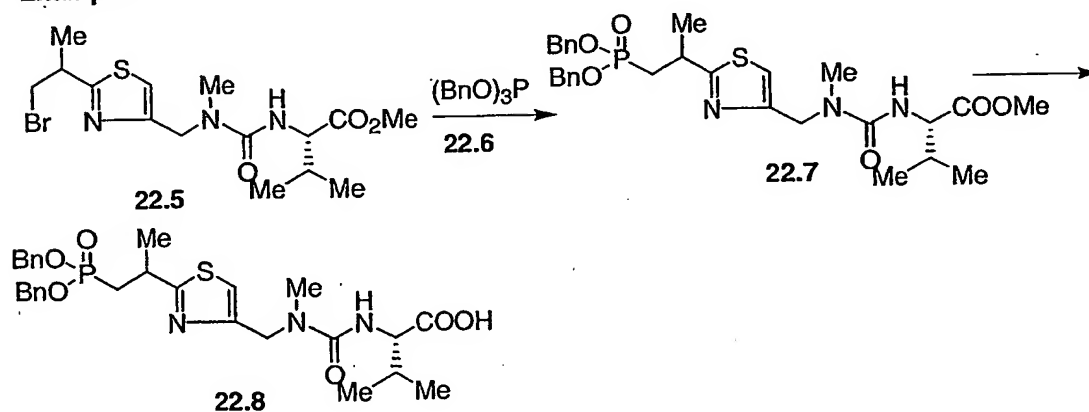
Using the above procedures, but employing, in place of the dialkyl mercaptoethyl phosphonate 26.15, different mercaptoalkyl phosphonates 26.12, the corresponding products 26.14 are obtained.

Scheme 22

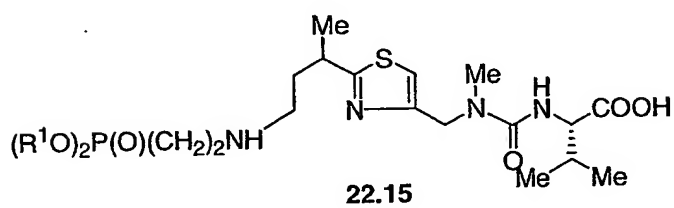
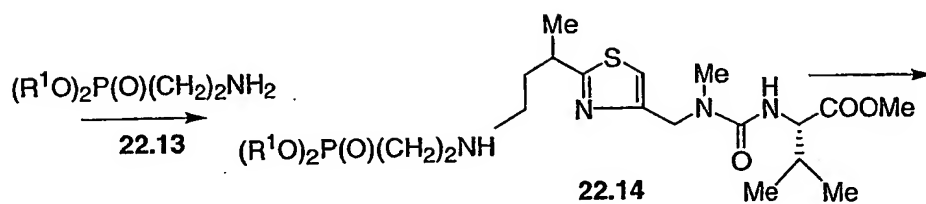
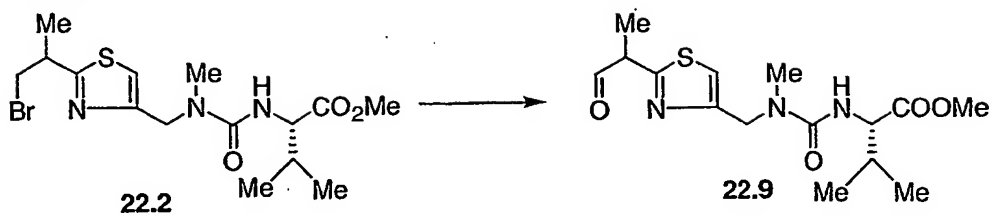
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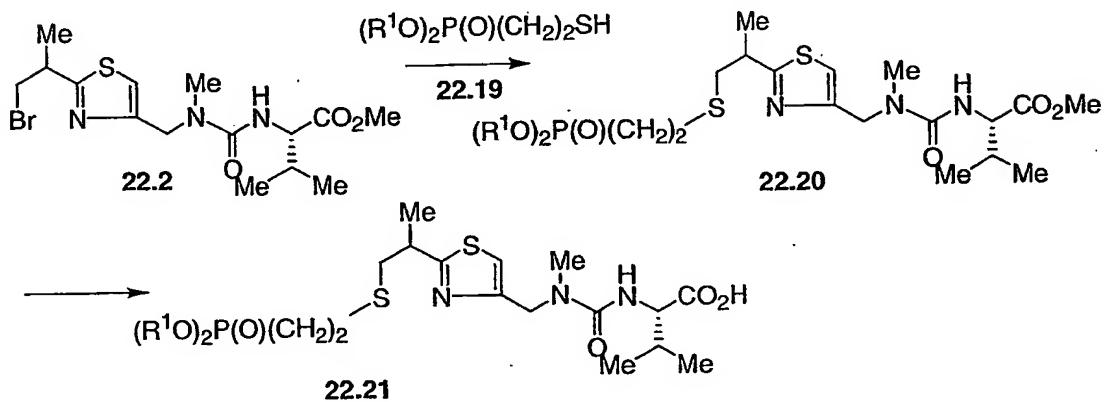
Example 1



Example 2

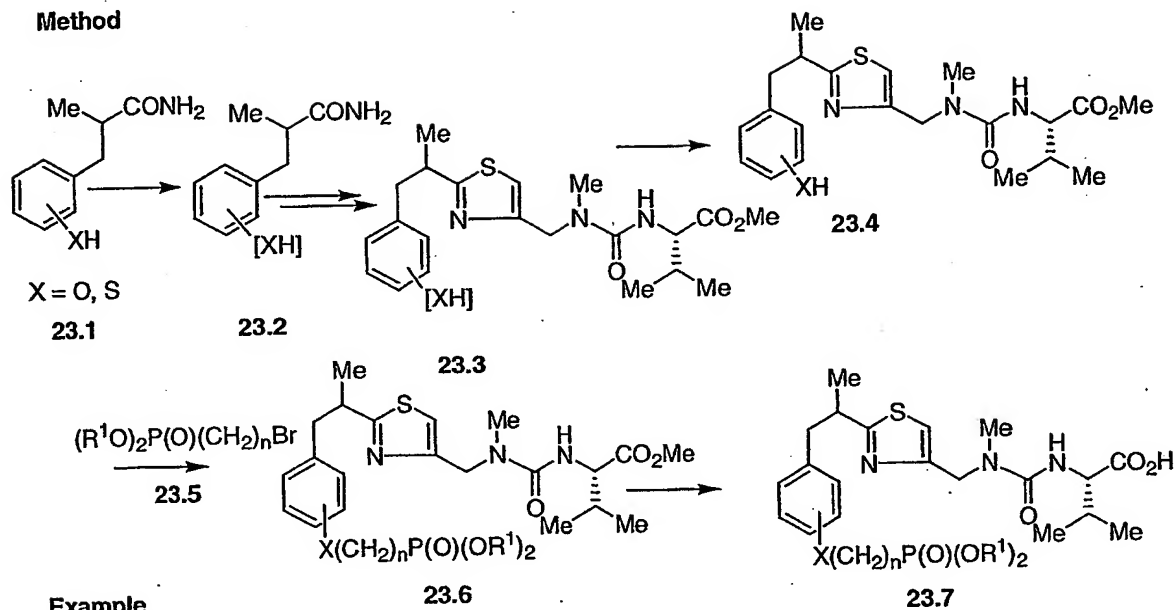


Example 3

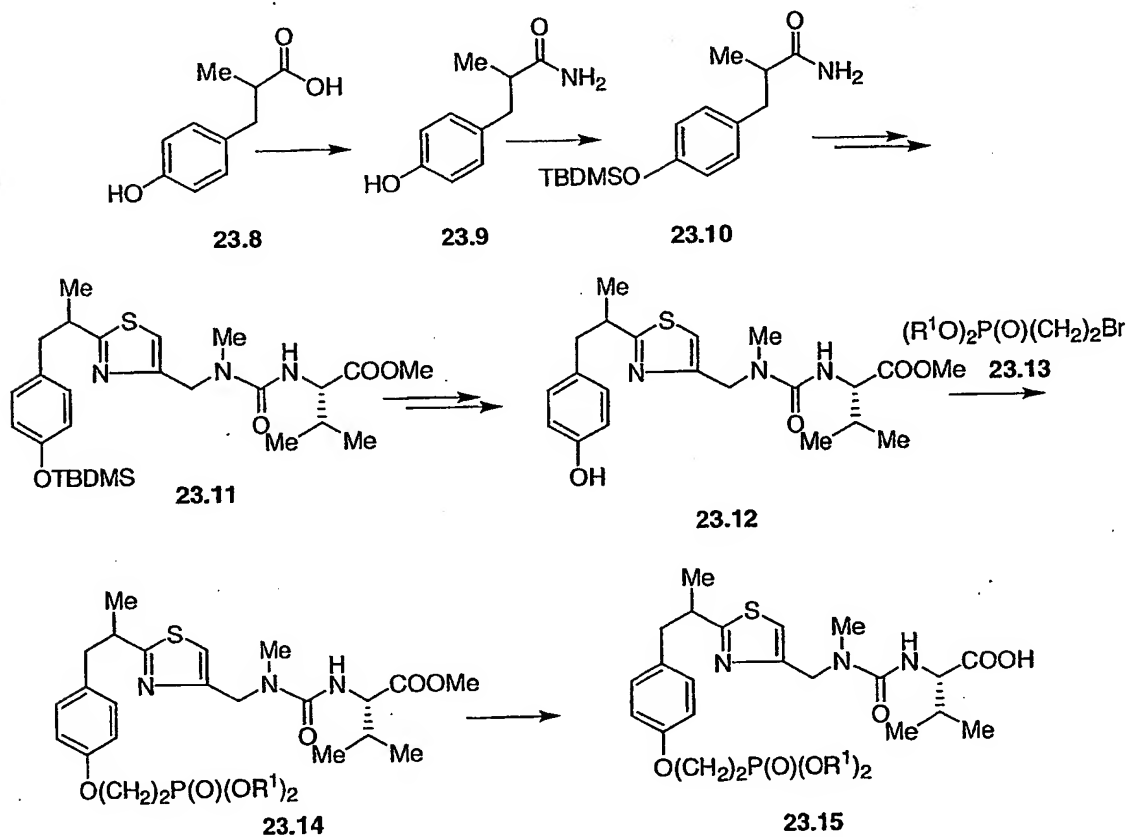


Scheme 23

Method

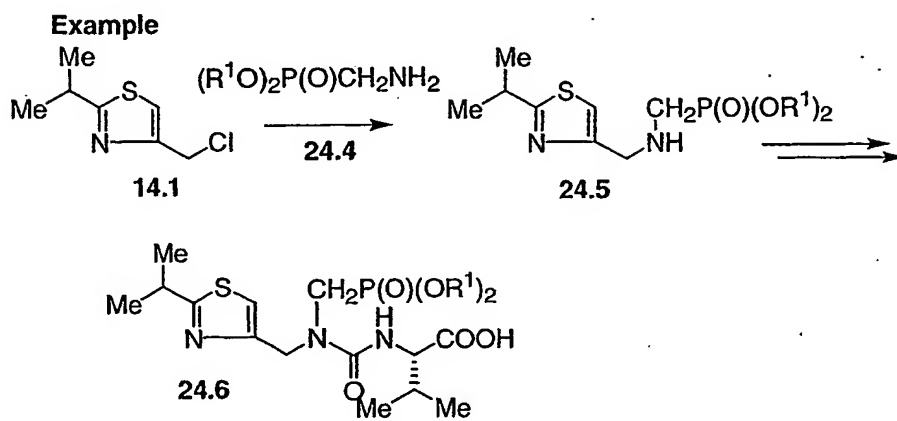
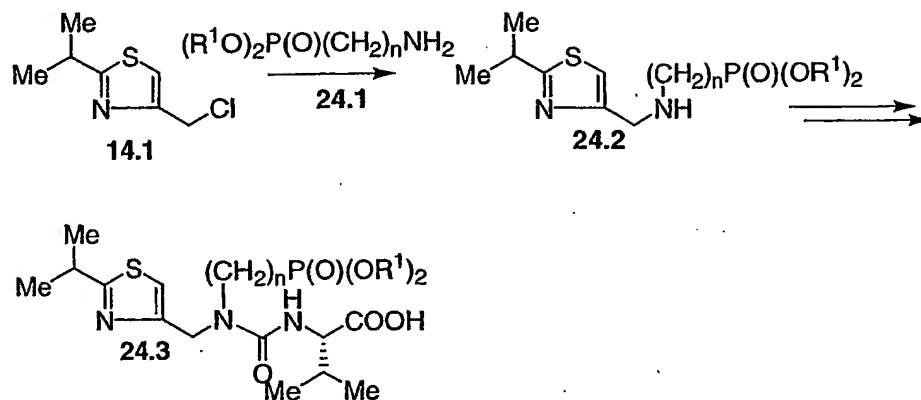


Example

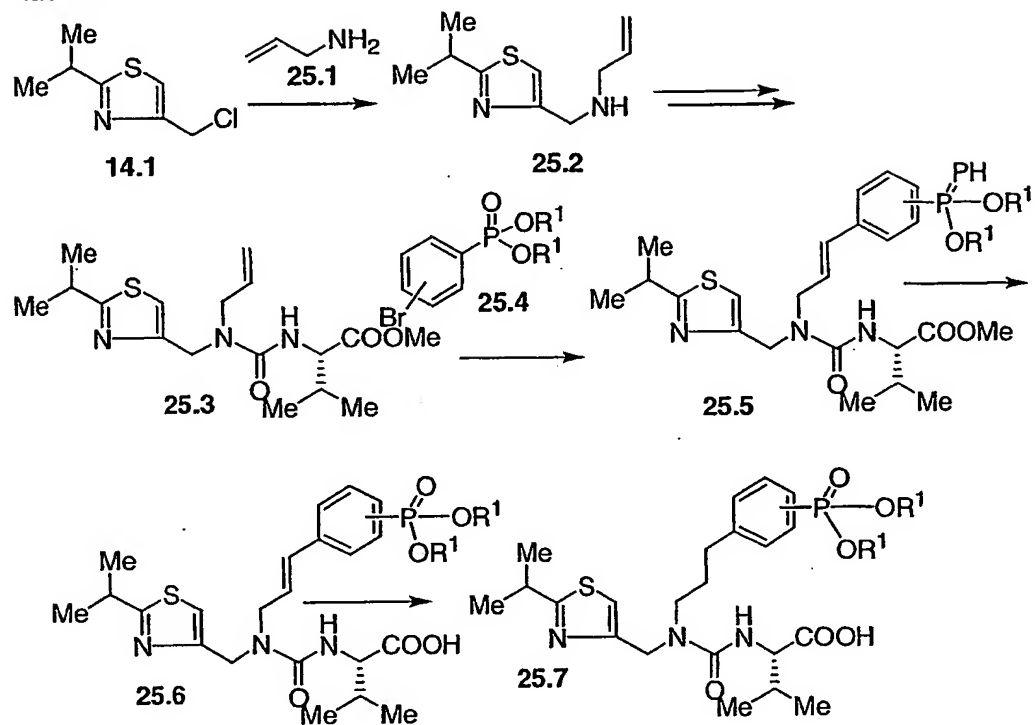


Scheme 24

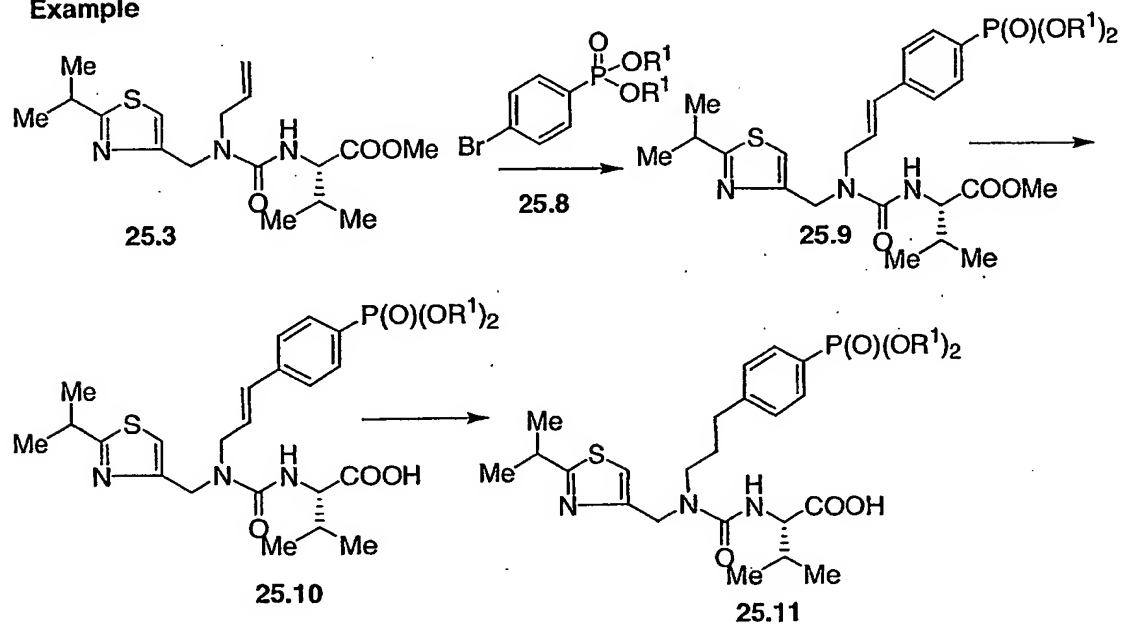
Method



Scheme 25
Method

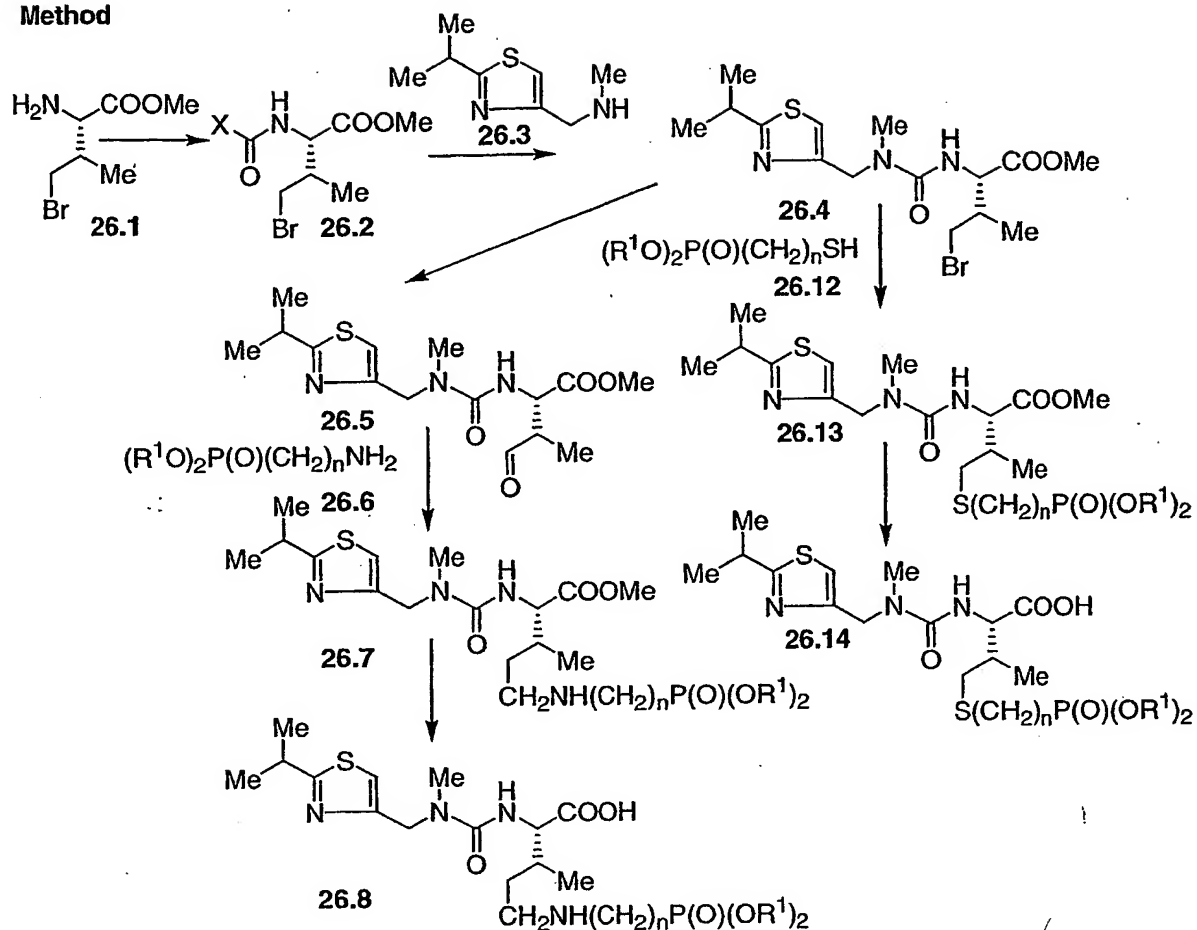


Example

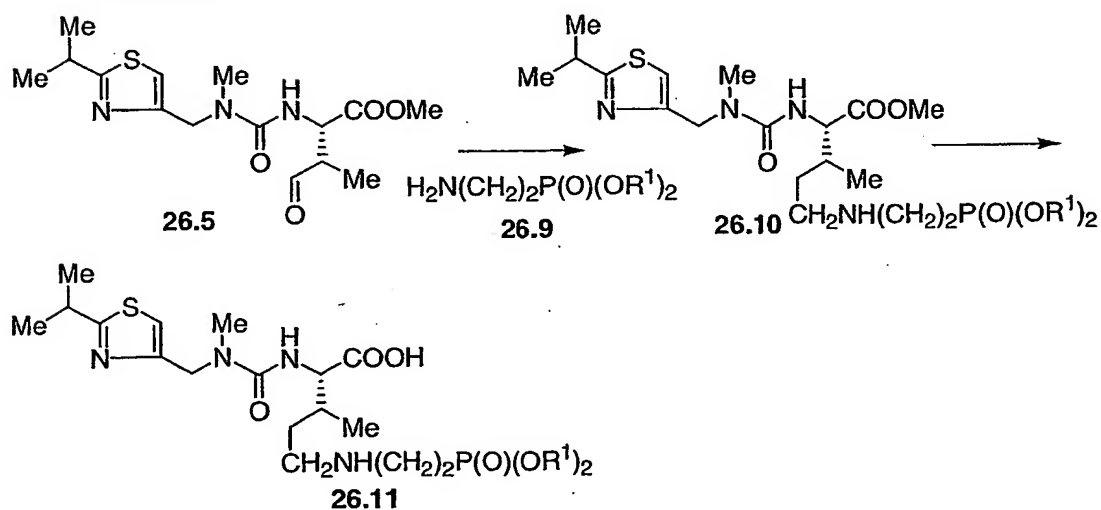


Scheme 26

Method



Example 1



Interconversions of the phosphonates R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

- 5 Schemes 1-26 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may be the same or different. The R¹ groups attached to a phosphonate esters 1-7, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 27. The group R in Scheme 27 represents
- 10 the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1-7 or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-7. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M.
- 15 Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

- The conversion of a phosphonate diester 27.1 into the corresponding phosphonate monoester 27.2 (Scheme 27, Reaction 1) can be accomplished by a number of methods. For example, the ester 27.1 in which R¹ is an aralkyl group such as benzyl, can be converted into the monoester compound 27.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO)
- 20 or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester 27.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 27.2 can be effected by treatment of the ester 27.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.
- 25 Phosphonate diesters 27.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 27.2 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, can be converted into the monoester 27.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in
- 30 aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by

using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

- The conversion of a phosphonate diester 27.1 or a phosphonate monoester 27.2 into the corresponding phosphonic acid 27.3 (Scheme 27, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 27.2 in which R¹ is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid 27.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester 27.2 in which R¹ is alkenyl such as, for example, allyl, can be converted into the phosphonic acid 27.3 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985.
- 15 Palladium catalyzed hydrogenolysis of phosphonate esters 27.1 in which R¹ is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters 27.1 in which R¹ is phenyl is described in J. Amer. Chem. Soc., 78, 2336, 1956.

- The conversion of a phosphonate monoester 27.2 into a phosphonate diester 27.1 (Scheme 27, Reaction 4) in which the newly introduced R¹ group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate 27.2 is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yl)oxytripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester 27.2 to the diester 27.1 can be effected by the use of the Mitsunobu reaction, as described above (Scheme 16). The substrate is reacted with the hydroxy compound R¹OH, in the presence of

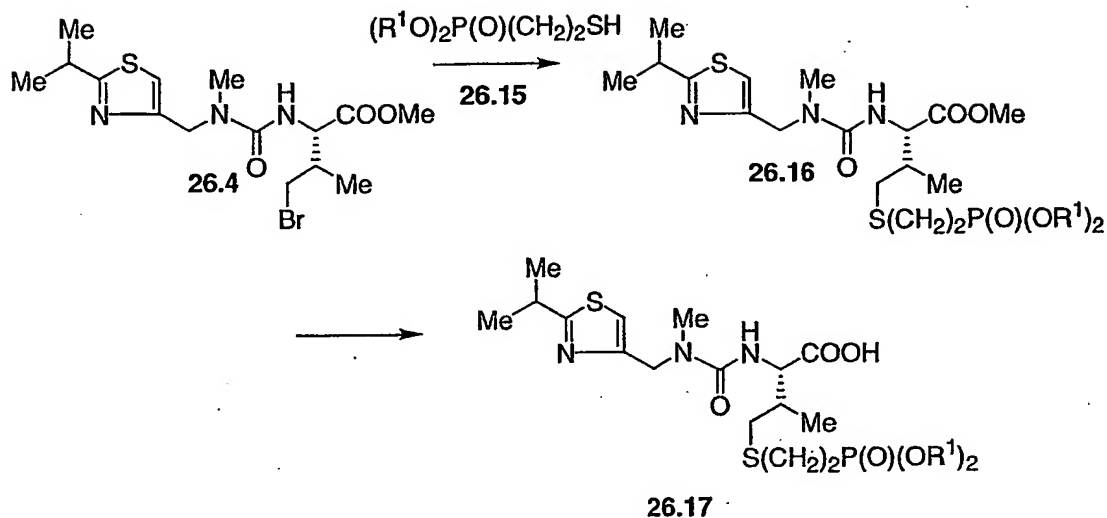
diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester 27.2 can be transformed into the phosphonate diester 27.1, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br , in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester 27.2 is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester 27.1.

A phosphonic acid $R\text{-link-P}(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme 27, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $R\text{-link-P}(O)(OR^1)_2$ 27.1, except that only one molar proportion of the component R^1OH or R^1Br is employed.

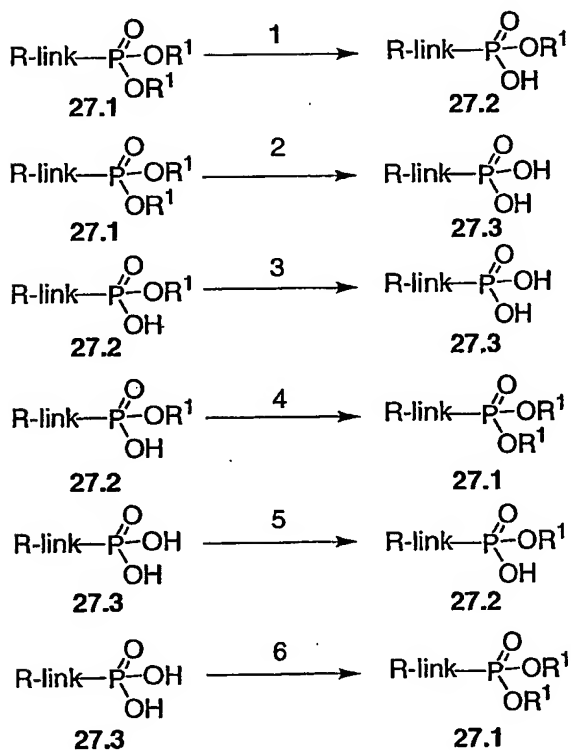
A phosphonic acid $R\text{-link-P}(O)(OH)_2$ 27.3 can be transformed into a phosphonate diester $R\text{-link-P}(O)(OR^1)_2$ 27.1 (Scheme 27, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids 27.3 can be transformed into phosphonic esters 27.1 in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°C. Alternatively, phosphonic acids 27.3 can be transformed into phosphonic esters 27.1 in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester 27.1.

Scheme 26

Example 2



Scheme 27



General applicability of methods for introduction of phosphonate substituents.

The procedures described above for the conversion of various functional groups into phosphonate moieties are of general application. For example, the methods described above for the introduction of phosphonate groups into the phenylalanine moiety, can, with
5 appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the thiazole compounds 1.5, 9.1 and 11.1, and for the preparation of the phosphonate esters 3. Similarly, the methods described above for the introduction of phosphonate groups into the thiazole compounds 1.5, 9.1 and 11.1 can, with appropriate
10 modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the phenylalanine intermediates 4.1 and for the preparation of the compounds 3.

Phosphonate esters 1-7 incorporating carbamate moieties.

The phosphonate esters 1-7 in which the R^2CO or R^3CO groups are formally derived from the carboxylic acid synthons 14-16, 19, 21, 22, 25, 34, 51 or 52 as shown in Charts 2a, 2b, and
15 2c, contain a carbamate moiety. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

20 Scheme 28 illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme 28, in the general reaction generating carbamates, a carbinol 28.1 is converted into the activated derivative 28.2 in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative 28.2 is then reacted with an amine 28.3, to afford the carbamate product 28.4. Examples 1 - 7 in
25 Scheme 28 depict methods by which the general reaction can be effected. Examples 8 - 10 illustrate alternative methods for the preparation of carbamates.

Scheme 28, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol 28.5. In this procedure, the carbinol 28.5 is reacted with phosgene, in an inert solvent such as toluene, at about 0°C, as described in Org. Syn. Coll. Vol. 3, 167,
30 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate 28.6. The latter compound is

then reacted with the amine component 28.3, in the presence of an organic or inorganic base, to afford the carbamate 28.7. cFor example, the chloroformyl compound 28.6 is reacted with the amine 28.3 in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate

5 28.7. cAlternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 28, Example 2 depicts the reaction of the chloroformate compound 28.6 with imidazole, 28.7, to produce the imidazolide 28.8. The imidazolide product is then reacted with the amine 28.3 to yield the carbamate 28.7. The preparation of the imidazolide is
10 performed in an aprotic solvent such as dichloromethane at 0°C, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 28 Example 3, depicts the reaction of the chloroformate 28.6 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 28.10. The reaction is
15 conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 28.19 - 28.24 shown in Scheme 28, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 28.19, N-hydroxysuccinimide 28.20, or pentachlorophenol, 28.21, the mixed carbonate 28.10 is obtained by the reaction of the
20 chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 28.22 or 2-hydroxypyridine 28.23 can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

25 Scheme 28 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 28.8 is employed. In this procedure, a carbinol 28.5 is reacted with an equimolar amount of carbonyl diimidazole 28.11 to prepare the intermediate 28.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 28.8 is then reacted with an equimolar amount of the
30 amine R'NH₂ to afford the carbamate 28.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 28.7.

Scheme 28, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole 28.13. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride 28.12, to afford the alkoxycarbonyl product 28.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine R'NH₂ to afford the carbamate 28.7. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80°C as described in Syn., 1977, 704.

Scheme 28, Example 6 illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, 28.14, is reacted with a carbinol 28.5 to afford the intermediate alkyloxycarbonyl intermediate 28.15. The latter reagent is then reacted with the amine R'NH₂ to afford the carbamate 28.7. The procedure in which the reagent 28.15 is derived from hydroxybenztriazole 28.19 is described in Synthesis, 1993, 908; the procedure in which the reagent 28.15 is derived from N-hydroxysuccinimide 28.20 is described in Tet. Lett., 1992, 2781; the procedure in which the reagent 28.15 is derived from 2-hydroxypyridine 28.23 is described in Tet. Lett., 1991, 4251; the procedure in which the reagent 28.15 is derived from 4-nitrophenol 28.24 is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate 28.14 is conducted in an inert organic solvent at ambient temperature.

Scheme 28, Example 7 illustrates the preparation of carbamates from alkoxycarbonyl azides 28.16. In this procedure, an alkyl chloroformate 28.6 is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide 28.16. The latter compound is then reacted with an equimolar amount of the amine R'NH₂ to afford the carbamate 28.7. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme 28, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate 28.7.

Scheme 28, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate 28.18. In this procedure, which is described in

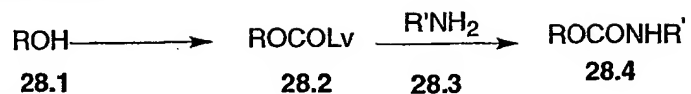
Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate 28.7.

Scheme 28, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine R'NH₂. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate 28.7.

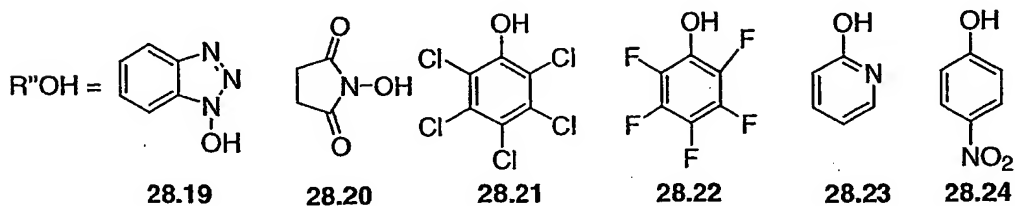
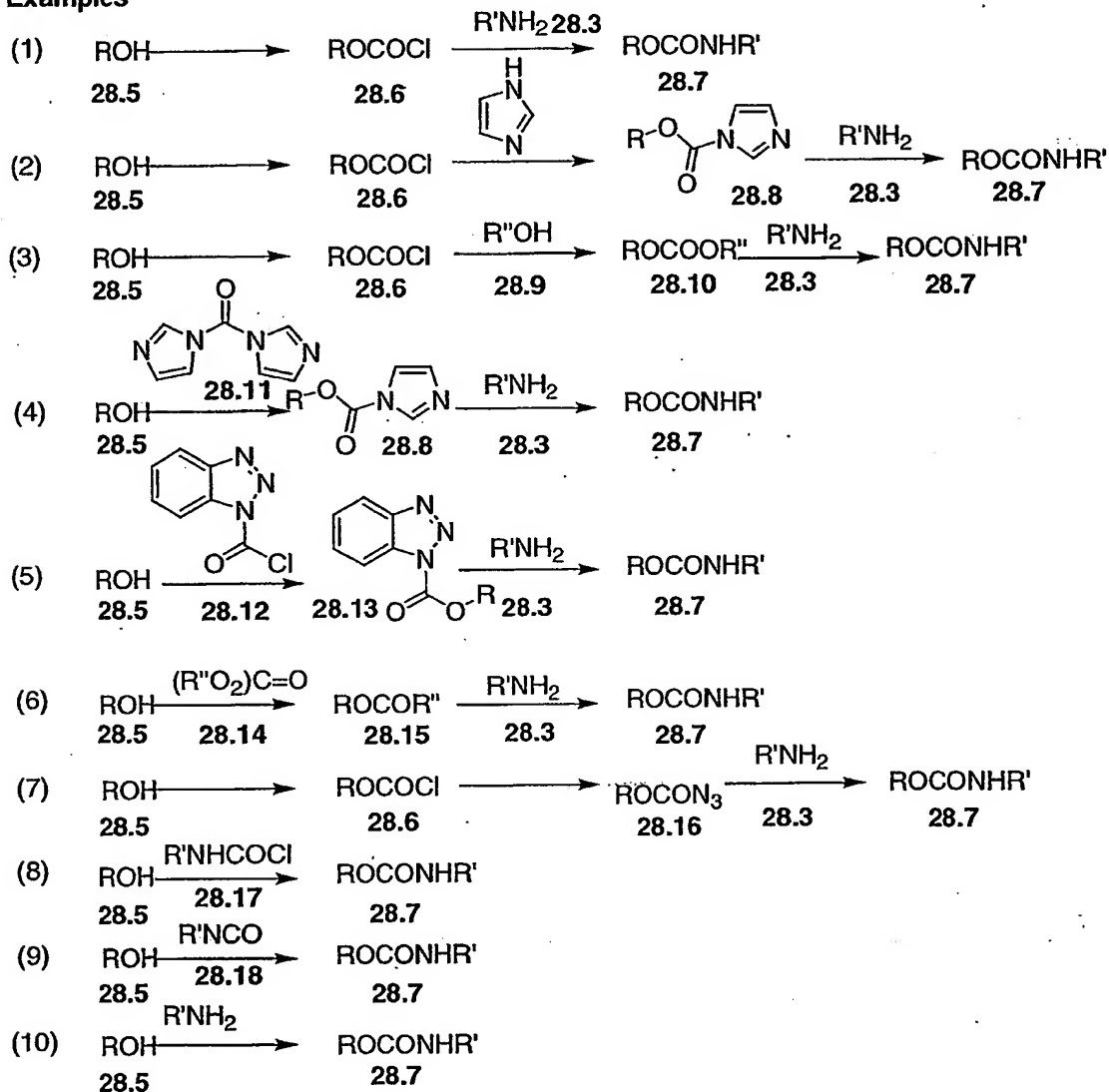
10

Scheme 28

General reaction



Examples



Preparation of phosphonate intermediates 6 and 7 with phosphonate moieties incorporated into the group R^2COOH and R^3COOH .

5 The chemical transformations described in Schemes 1-28 illustrate the preparation of compounds 1-5 in which the phosphonate ester moiety is attached to the thiazole substructure, (Schemes 1-3, 9-10, and 11-12), the phenylalanine moiety (Schemes 4-6), and the benzyl moiety (Schemes 7-8).

The various chemical methods employed for the preparation of phosphonate groups can, with
10 appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R^2COOH and R^3COOH , as defined in Charts 2a, 2b and 2c. The resultant phosphonate-containing analogs, designated as $R^{2a}COOH$ and $R^{3a}COOH$ can then, using the procedures described above, be employed in the preparation of the compounds 6 and 7. The procedures required for the introduction of the phosphonate-
15 containing analogs $R^{2a}COOH$ and $R^{3a}COOH$ are the same as those described above (Schemes 4, 5, and 28) for the introduction of the R^2CO and R^3CO moieties.

Indinavir-like phosphonate protease inhibitors (ILPPI)

20 **Preparation of the intermediate phosphonate esters 1-24.**

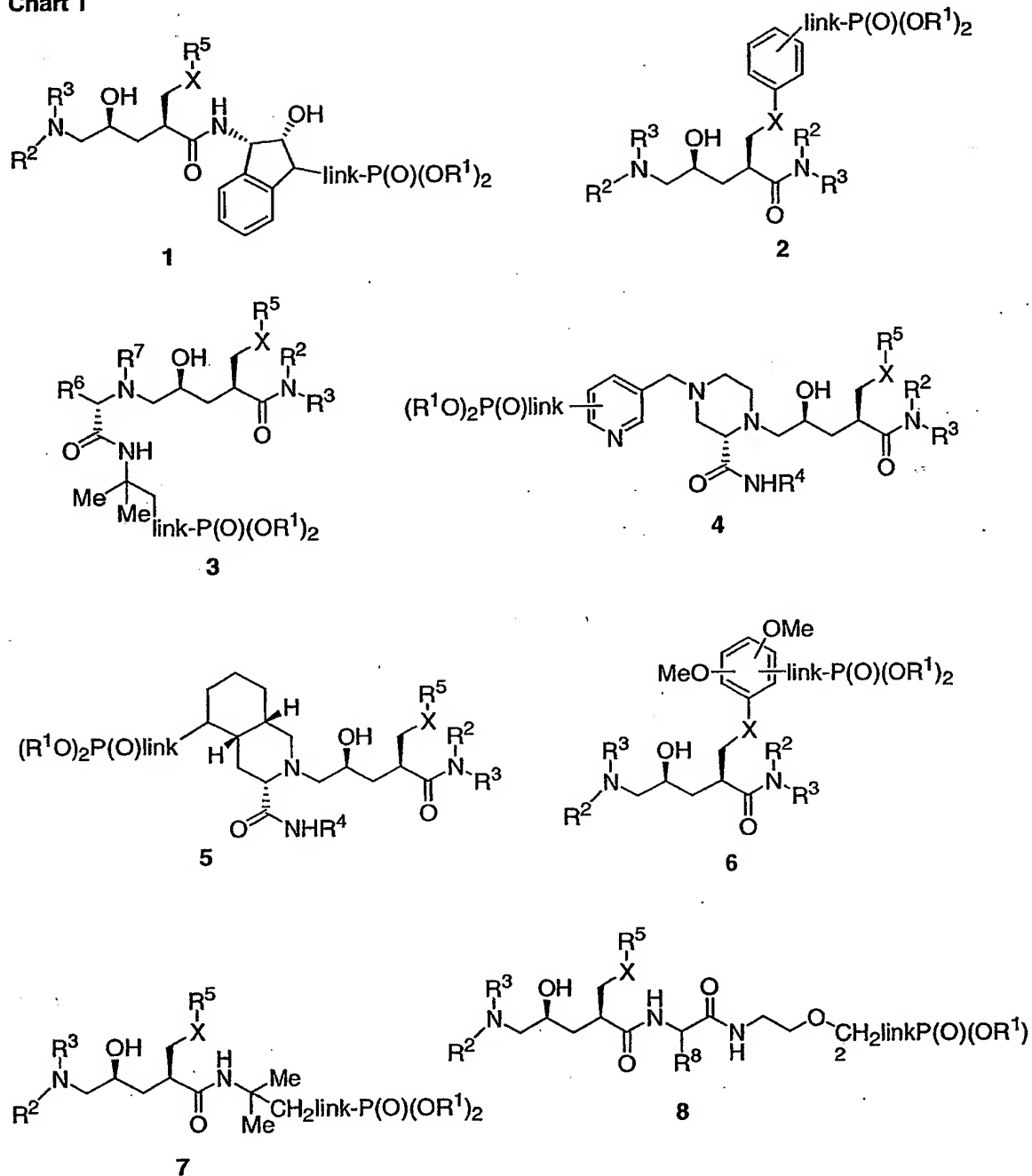
The structures of the intermediate phosphonate esters 1 to 22 and the structures of the component groups R^1 , R^4 , R^8 , R^9 , R^{11} , X and X' of this invention are shown in Charts 1 - 3. The structures of the R^2R^3NH components are shown in Chart 4; the structures of the amines
25 components $R^7NHCH(R^6)CONHR^4$ are shown as the structures A1 - A16 in Chart 4. The structures of the R^5XCH_2 groups are shown in Chart 5, and those of the $R^{10}CO$ components are illustrated in Chart 6. The structures of the $R^7NHCH(R^6)COOH$ components are shown in Chart 10.

Specific stereoisomers of some of the structures are shown in Charts 1 - 10; however, all
30 stereoisomers are utilized in the syntheses of the compounds 1 to 24. Subsequent chemical modifications to the compounds 1 to 24, as described herein, permit the synthesis of the final compounds of this invention.

The intermediate compounds **1** to **24** incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **7**, **8** and **9** illustrate examples of the linking groups present in the structures **1** – **24**.

- 5 Schemes **1** - **207** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1** - **22**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **23** and **24**, in which a phosphonate moiety is incorporated into one of the groups R^2 , R^3 , R^5 , R^{10} or R^{11} is also described below. In compounds **2**, **6**, **23** and **24** where two groups are the same Chart **4** it is noted that these
- 10 groups may be independent or identical.

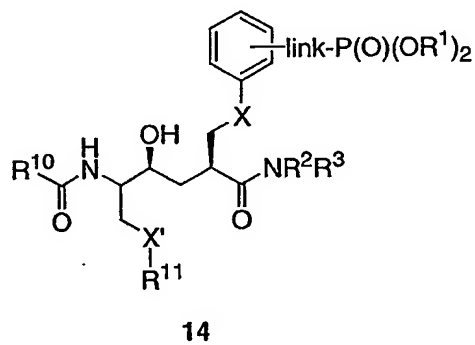
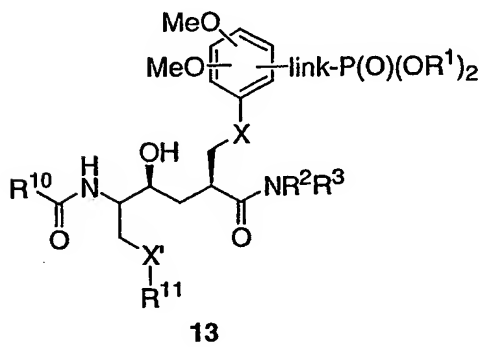
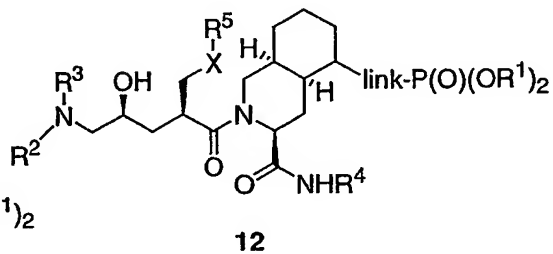
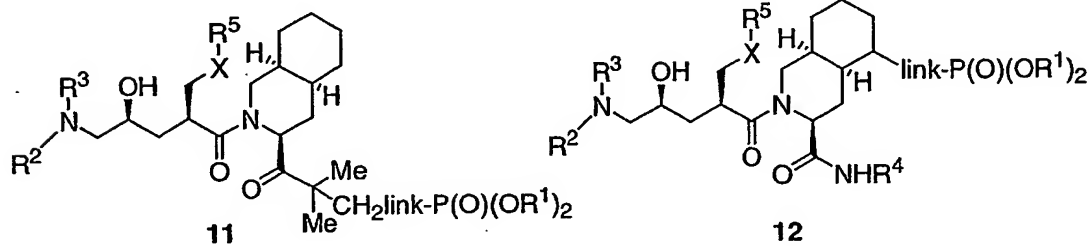
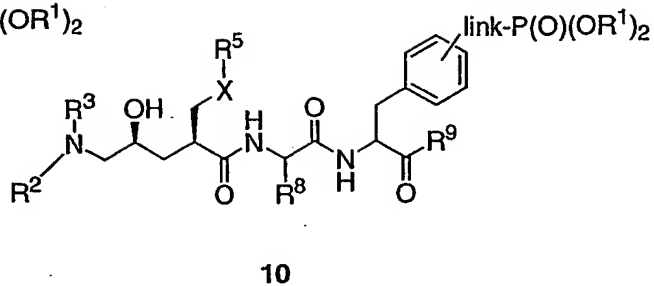
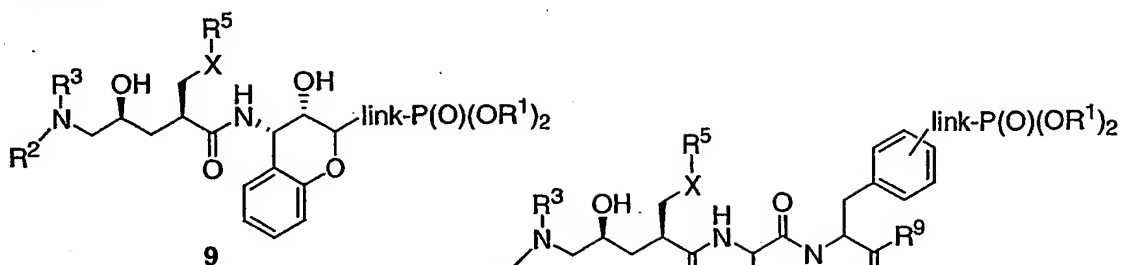
Chart 1

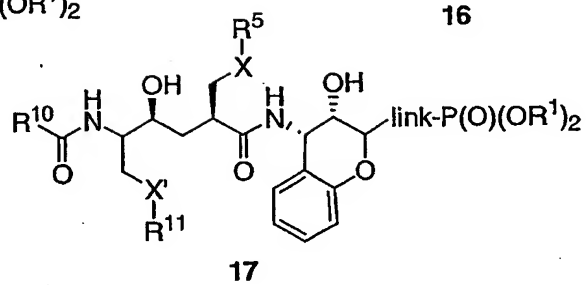
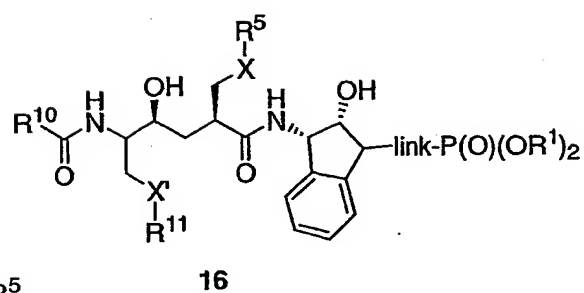
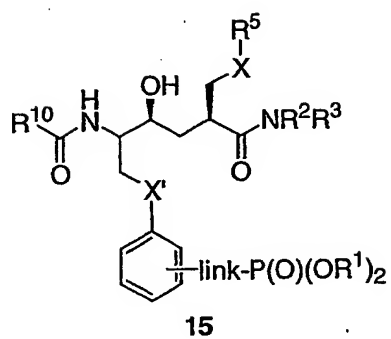


$R^1 = H, \text{ alkyl, haloalkyl, alkenyl, aralkyl, aryl}$

$$R^4 = CH(CH_3)_3; CH_2CF_3; CH_2C_6H_4(CH_3)-2; CH_2C_6H_3(CH_3)_2 \text{ 2,6}$$

Chart 2





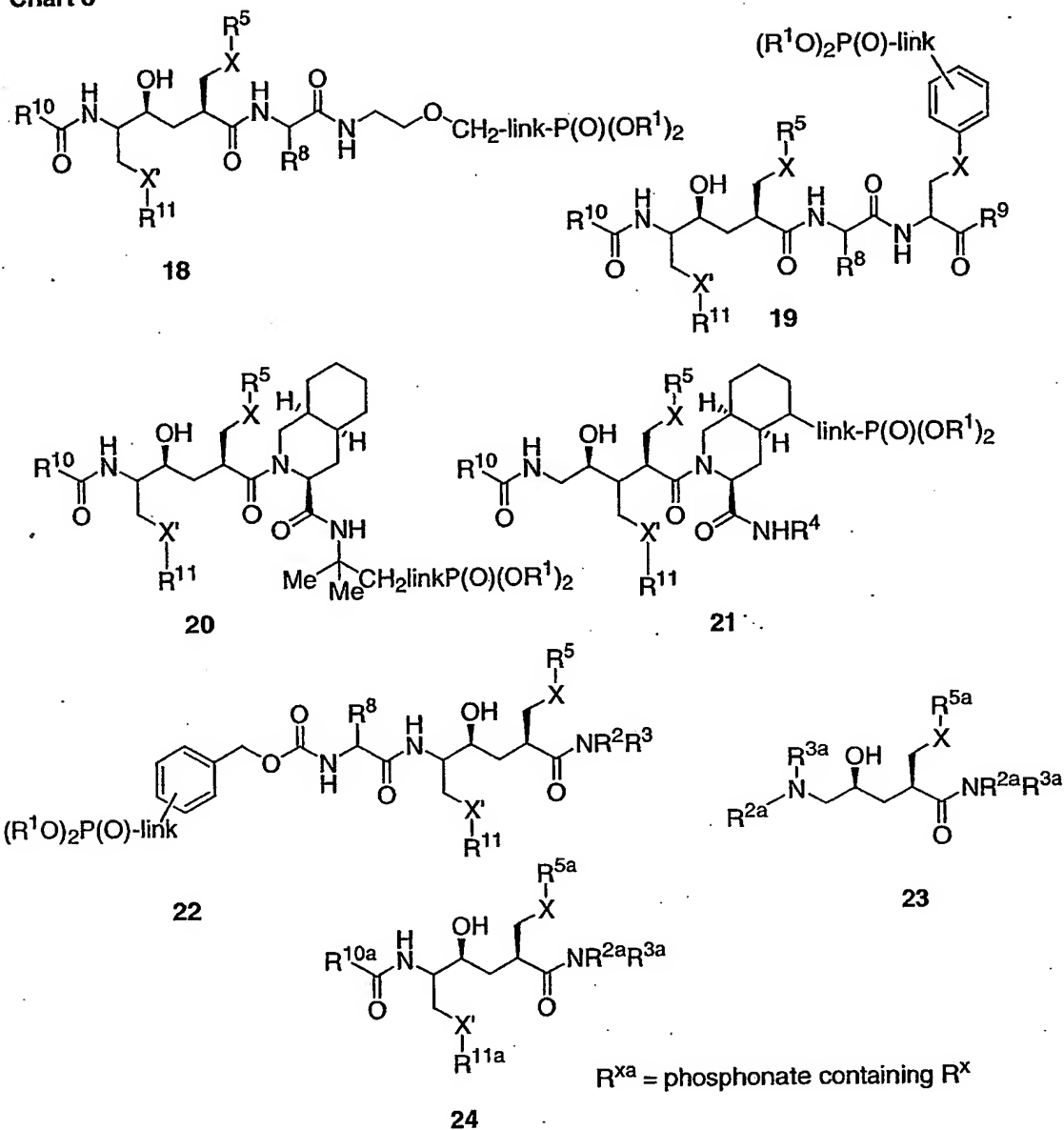
R¹¹ = phenyl, alkyl

R¹ = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R⁴ = CH(CH₃)₃; CH₂CF₃; CH₂C₆H₄(CH₃)₂; CH₂C₆H₃(CH₃)₂ 2,6

R⁹ = morpholino or methoxy

Chart 3



R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^4 = $C(CH_3)_3$; CH_2CF_3 ; $CH_2C_6H_4(CH_3)_2$; $CH_2C_6H_3(CH_3)_2$ 2,6

R^8 = alkyl, $CH_2SO_2CH_3$, $C(CH_3)_2SO_2CH_3$, CH_2CONH_2 , CH_2SCH_3 , imidaz-4-ylmethyl, CH_2NHAc , $CH_2NHCOCF_3$

R^9 = morpholino; alkoxy.

R^{11} = phenyl, alkyl

X, X' = S, direct bond

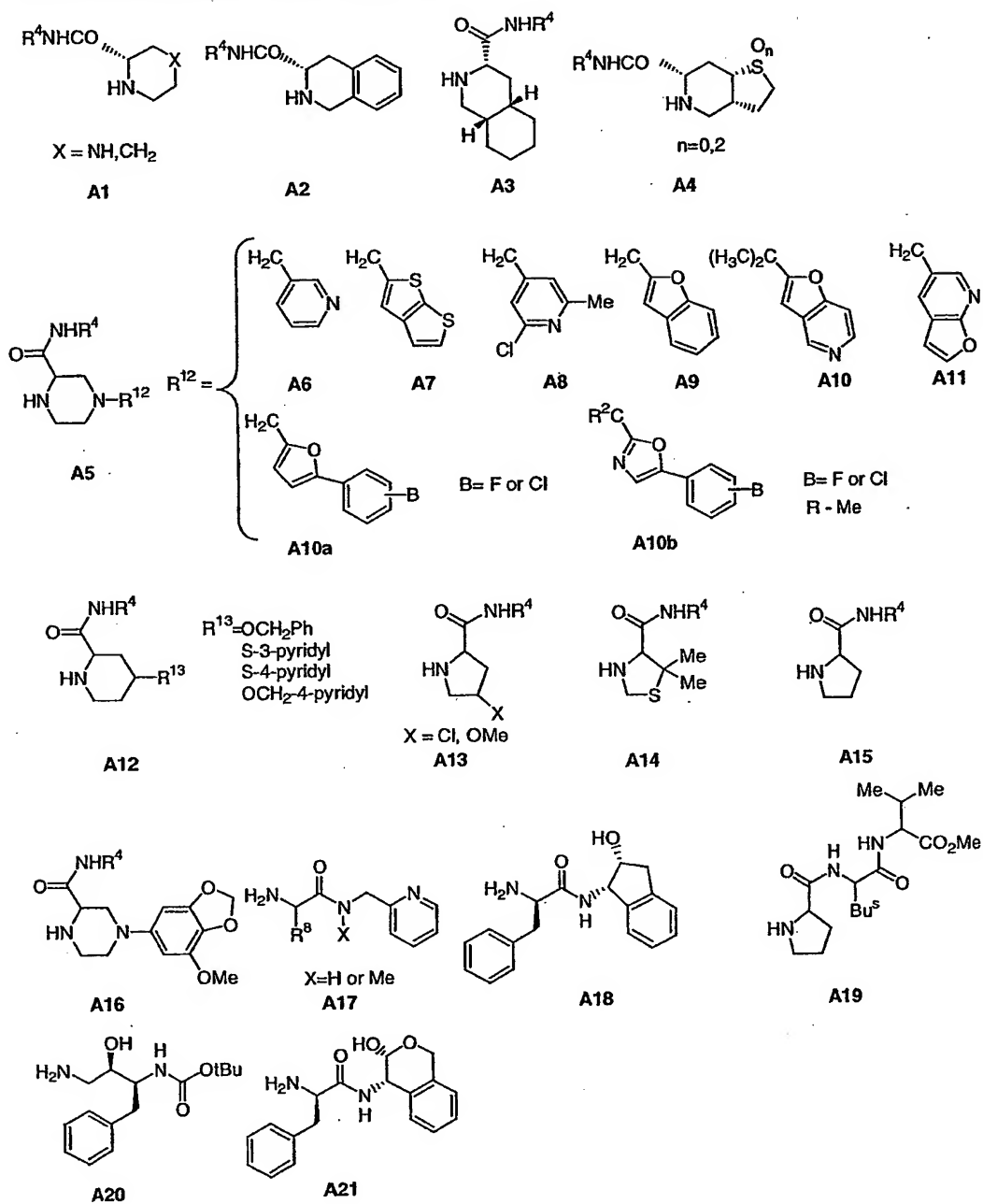
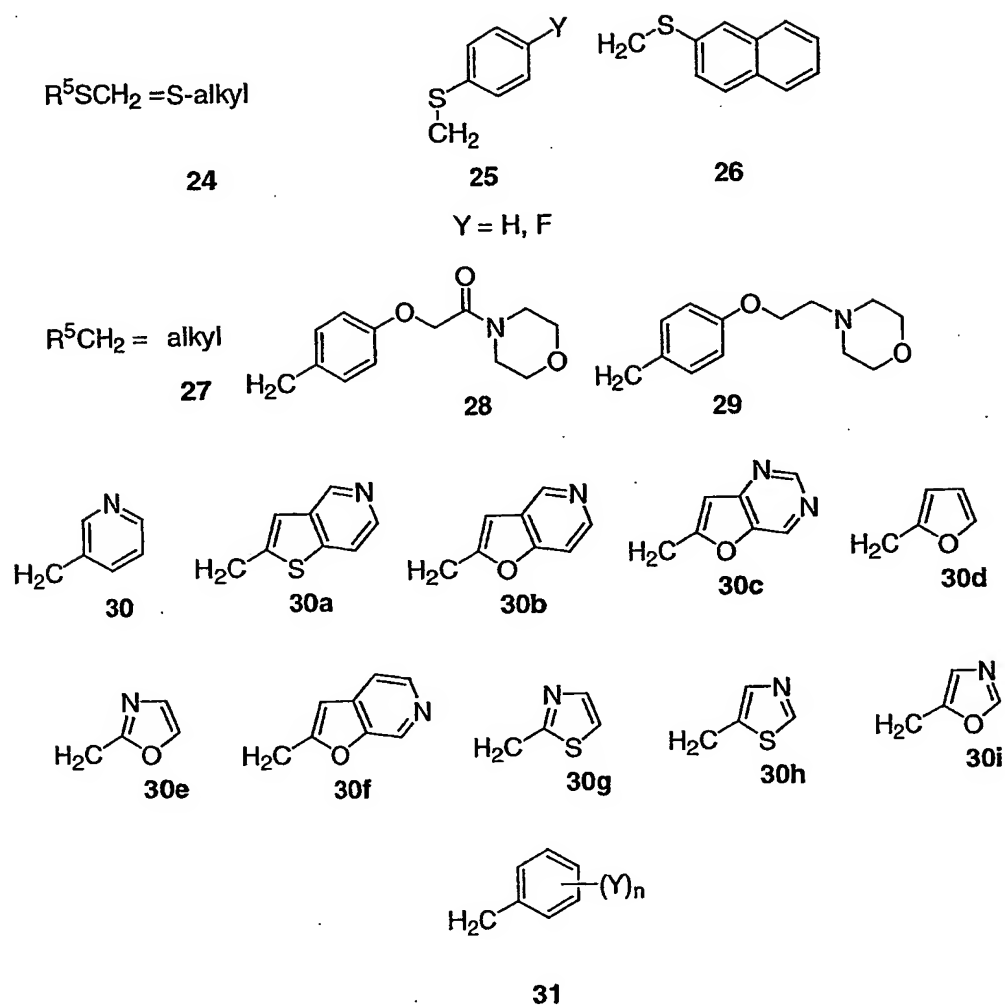
Chart 4 Structures of the R^2R^3NH components

Chart 5. Structures of the R^5XCH_2 groups.

$Y = H, OC_2H_5, OCH_2C_6H_5, MeO, (MeO)_2, (MeO)_3, CH_2CH_2OH, OH, Ha, CN, Ph, OCH_2O, OCH_2Ph$

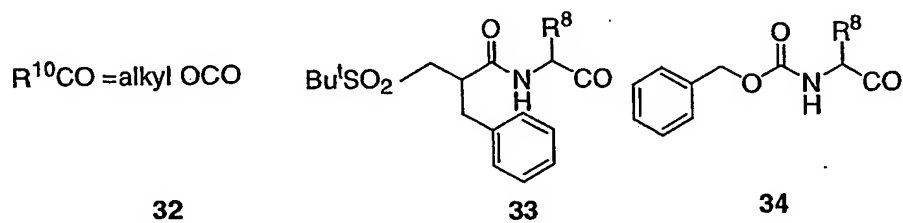
Chart 6. Structures of the $R^{10}CO$ components

Chart 7. Examples of linking groups

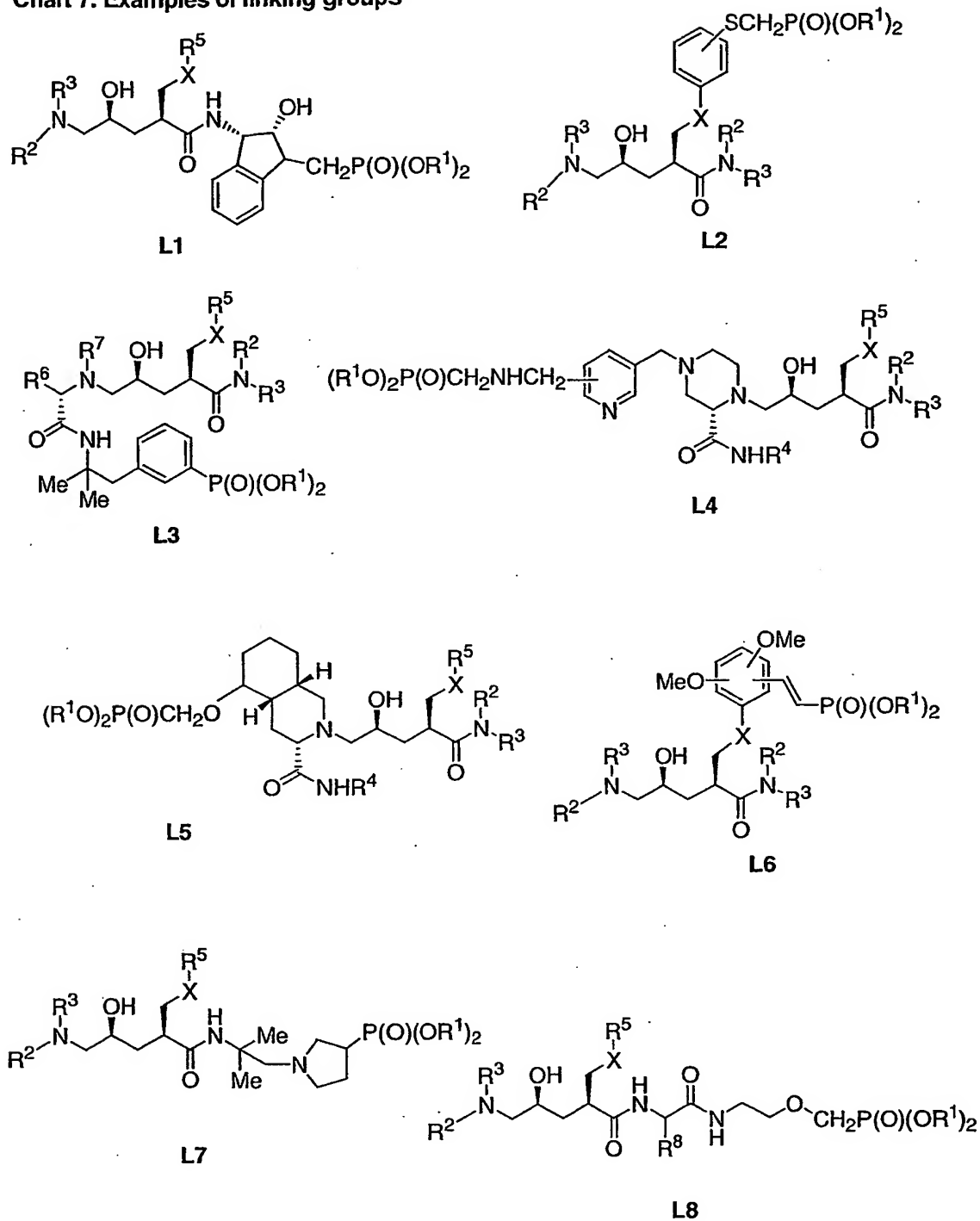


Chart 8. Examples of linking groups

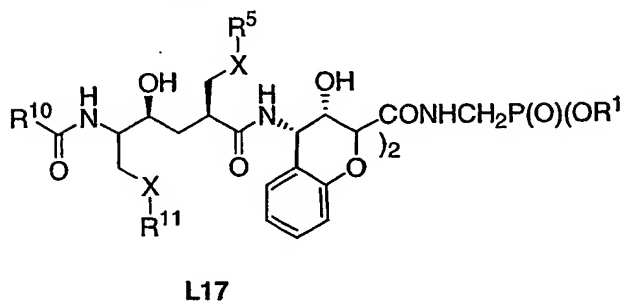
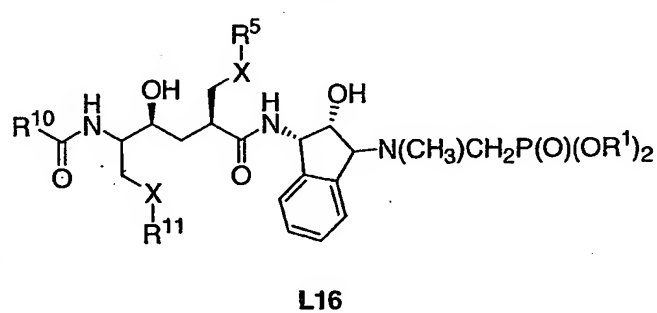
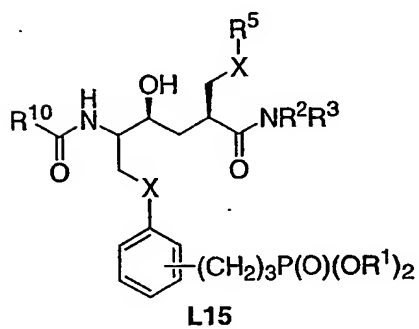
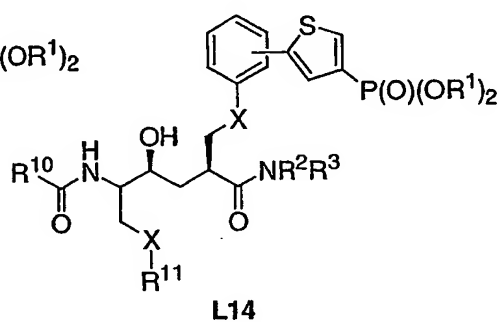
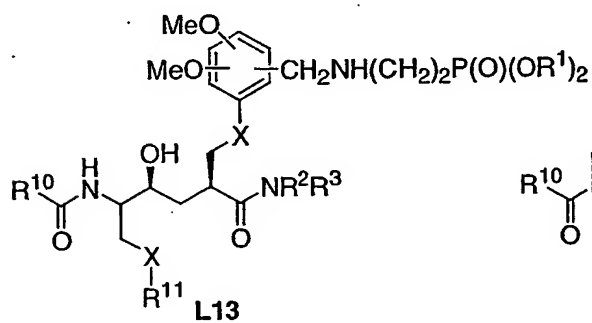
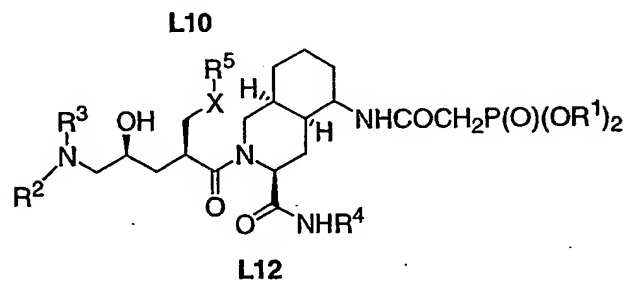
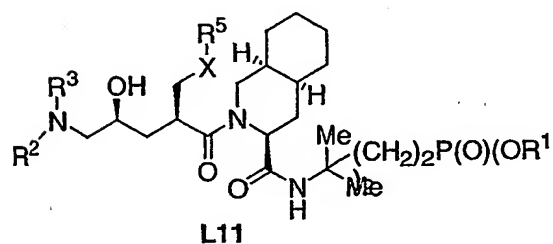
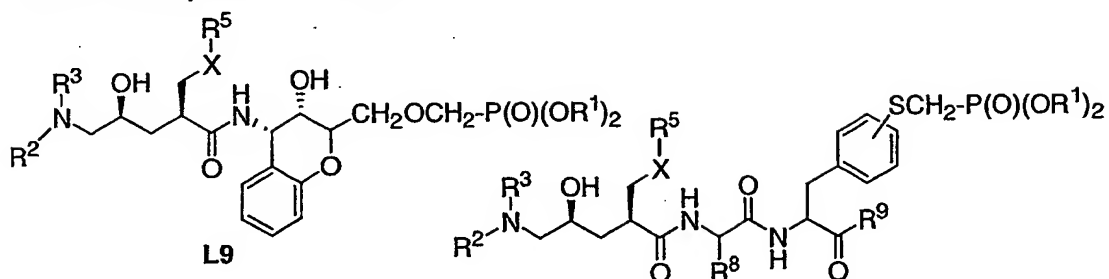


Chart 9. Examples of linking groups

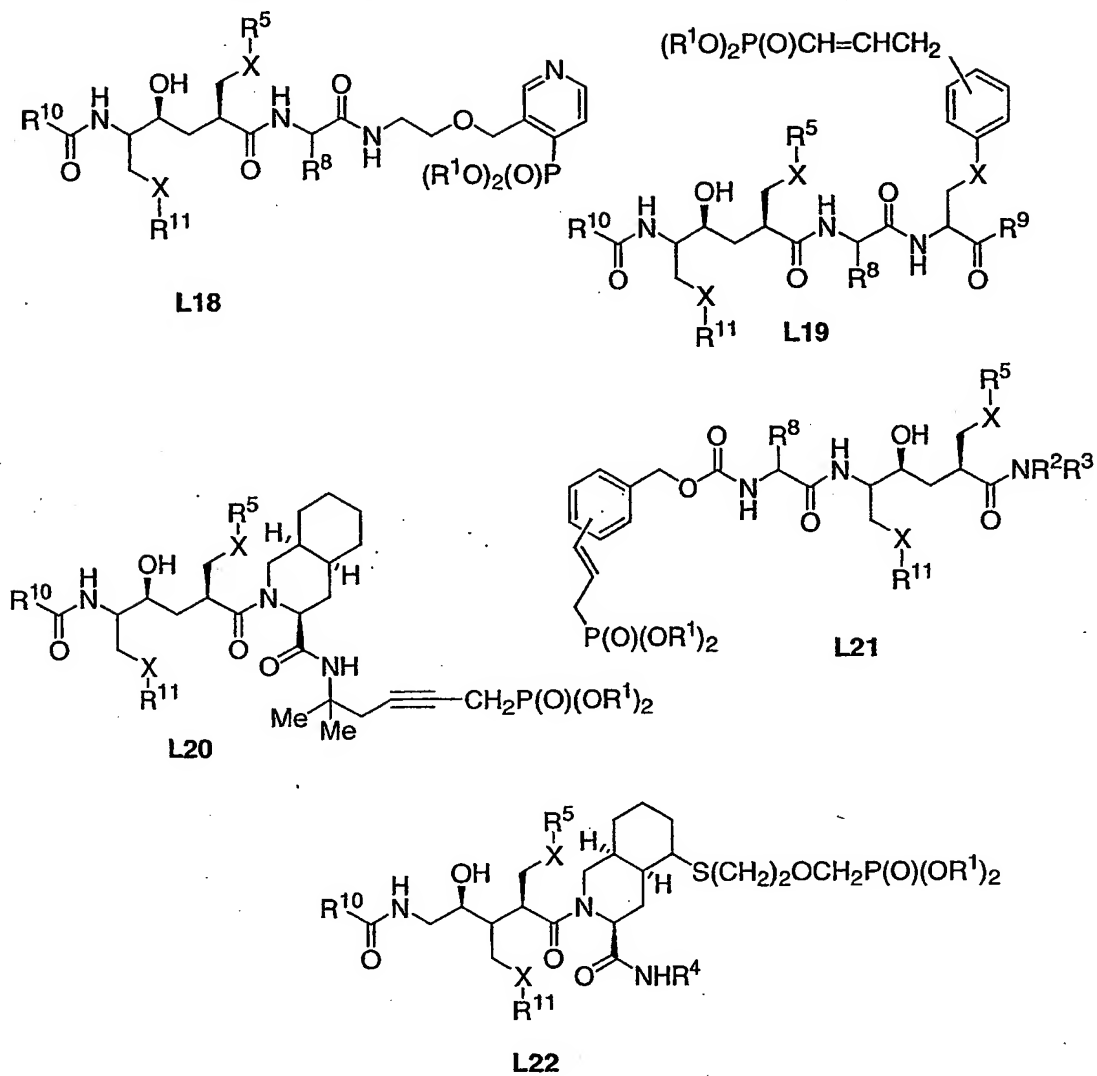
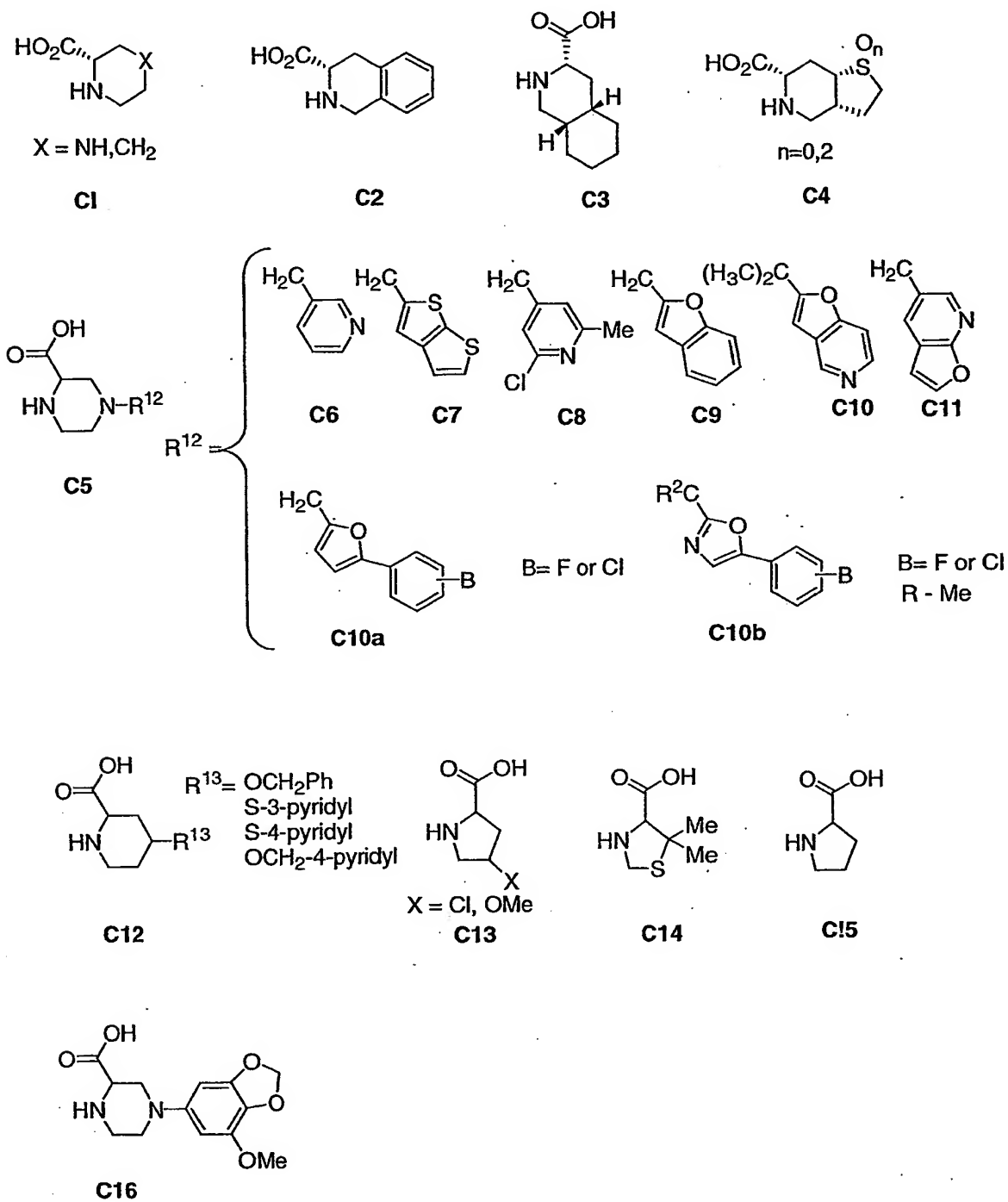


Chart 10. Structures of the $R^7NHCH(R^6)COOH$ components

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain
5 reactive substituents from unwanted reactions by protection before the sequence described,
and to deprotect the substituents afterwards, according to the knowledge of one skilled in the
art. Protection and deprotection of functional groups are described, for example, in Protective
Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990.
Reactive substituents which may be protected are shown in the accompanying schemes as, for
10 example, [OH], [SH].

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

The intermediate phosphonate esters 1, in which the group A is attached to the aminoindanol
15 moiety, are prepared as shown in Schemes 1 and 2.

In this procedure, the propionic acid 1.1, or an activated derivative thereof, is reacted with an
aminoindanol derivative 1.2, in which the substituent A is either the group link-P(O)(OR¹)₂ or
a precursor such as [OH], [SH], [NH], Br, to afford the amide 1.3. The preparation of the
aminoindanol derivatives 1.2 is described in Schemes 133 - 137.

20 The preparation of amides from carboxylic acids and derivatives is described, for example, in
Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968,
p. 274. The carboxylic acid is reacted with the amine in the presence of an activating agent,
such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the
presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example,
25 pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as
the acid chloride or anhydride, and then reacted with the amine, in the presence of an organic
base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride is effected by
30 treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl
chloride in an inert organic solvent such as dichloromethane.

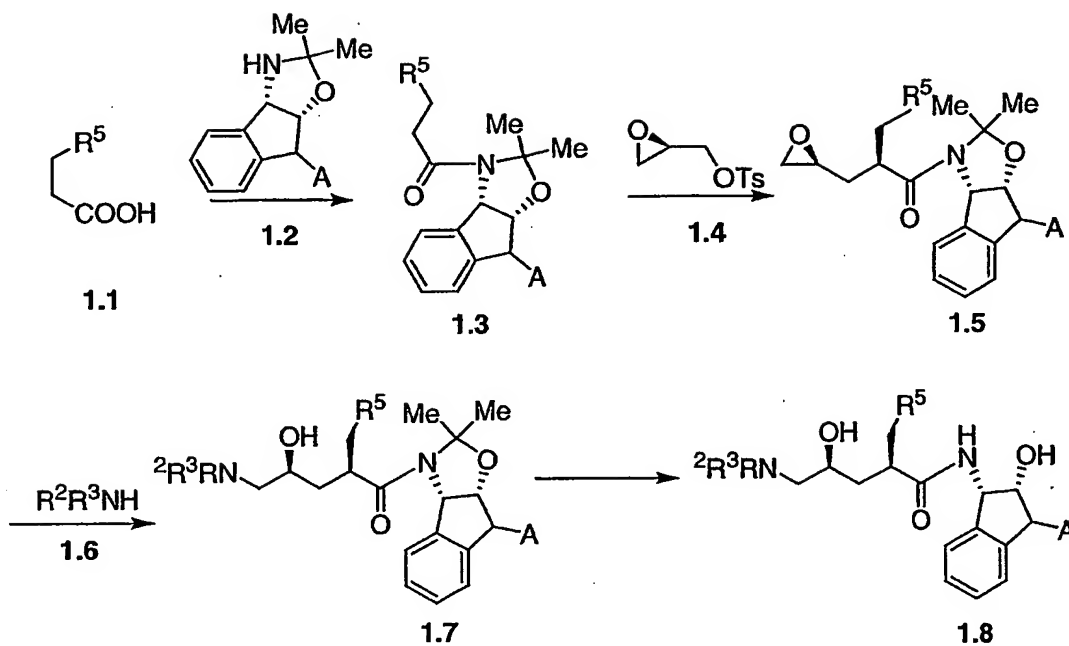
Preferably, the carboxylic acid **1.1** is reacted with an equimolar amount of the amine **1.2** in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, in an aprotic solvent such as, for example, tetrahydrofuran, at about ambient temperature, so as to afford the amide product **1.3**. The amide is then reacted with 2-(S)glycidyl tosylate **1.4**, or an equivalent thereof, such as, for example, 2-(S) glycidyl p-nitrobenzenesulfonate, as described in Tet Lett., 35, 673, 1994. To effect the reaction, the amide **1.3** is first converted into the α -anion, by treatment with a strong base, such as, for example, sodium hydride, potassium tert. butoxide and the like. The anion is then reacted with the epoxide **1.4**, or an equivalent, as described above, in an inert solvent such as, for example, dimethylformamide, dioxan and the like. The reaction is conducted at a temperature of from 0°C to -100°C to yield the alkylated product **1.5**. Preferably, equimolar amounts of the amide **1.3** and the epoxide **1.4** are dissolved in tetrahydrofuran at about -50°C, and a slight excess of lithium hexamethyldisilylazide is added, as described in WO 9612492 and Tet. Lett., 35, 673, 1994. The temperature is raised to about -25°C to effect stereoselective alkylation and conversion to the epoxide **1.5**. The thus-obtained epoxide **1.5** is then subjected to a regiospecific ring-opening reaction with the amine **1.6** to yield the hydroxyamine **1.7**. The preparation of hydroxyamines by the reaction between an amine and an epoxide is described, for example, in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1968, p. 357. The amine and the epoxide are reacted together in a polar organic solvent such as, for example, dimethylformamide or an alcohol, to effect the ring-opening reaction. Preferably, equimolar amounts of the amine **1.6** and the epoxide **1.5** are heated in isopropanol at reflux for about 24 hours, to prepare the hydroxyamine product **1.7**, for example as described in WO 9628439 and Tet. Lett., 35, 673, 1994. The hydroxyamine product **1.7** is then deprotected to remove the acetonide group and produce the compound **1.8** in which A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Acetonide protecting groups are removed by treatment with an acid, for example acetic acid or dilute hydrochloric acid, optionally in the presence of water and a water-miscible organic solvent such as, for example, tetrahydrofuran or an alcohol. Preferably, the acetonide protecting group is removed by treatment of the acetonide **1.7** with 6N hydrochloric acid in isopropanol at ambient temperature, as described in WO 9612492, to afford the indanol **1.8**.

The reactions shown in Scheme 1 illustrate the preparation of the compounds 1.8 in which A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 2 depicts the conversion of the compounds 1.8 in which A is [OH], [SH], [NH], Br, into the compounds 1 in which A is the group link-P(O)(OR¹)₂. In this procedure, the compounds 1.7 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 2.1. Deprotection, by removal of the acetonide protecting group, as described above, then affords the intermediate phosphonate esters 1 in which X is a direct bond.

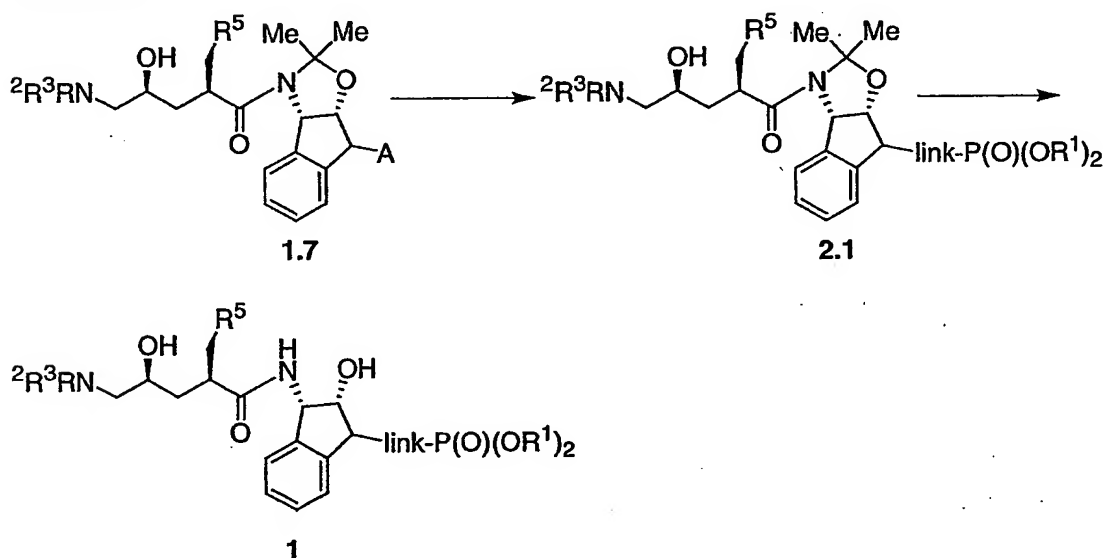
In the preceding and following schemes, the conversion of various substituents into the group link-P(O)(OR¹)₂ can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, during the introduction of the group link-P(O)(OR¹)₂.

In the preceding and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 199).

Scheme 1



Scheme 2



Preparation of the phosphonate ester intermediates 1 in which X is sulfur.

- 5 Schemes 3 and 4 illustrate the preparation of the phosphonate esters 1 in which X is sulfur. As shown in Scheme 3, methyl 2-allyl-3-hydroxypropionate 3.1, prepared as described in Tet. Lett., 1973, 2429, is converted into the benzyl ether 3.2. The conversion of alcohols into

benzyl ethers is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 47. The reaction is effected by treatment of the carbinol with a benzyl halide, in the presence of a base such as potassium hydroxide, silver oxide, sodium hydride and the like, in an organic or aqueous organic solvent, optionally in the presence of a phase transfer catalyst. Preferably, the carbinol 3.1 is reacted with benzyl bromide and silver oxide in dimethylformamide at ambient temperature for 48 hours, to afford the product 3.2. The benzyl ether is then subjected to an epoxidation reaction to produce the epoxide 3.3. The conversion of olefins into epoxides is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 456. The reaction is performed by the use of a peracid such as peracetic acid, m-chloroperbenzoic acid or monoperphthalic acid, optionally in the presence of a base such as potassium carbonate or sodium bicarbonate, or by the use of tert. butyl hydroperoxide, optionally in the presence of a chiral auxiliary such as diethyl tartrate. Preferably, equimolar amounts of the olefin and m-chloroperbenzoic acid are reacted in dichloromethane in the presence of sodium bicarbonate, as described in Tet. Lett., 849, 1965, to afford the epoxide 3.3. This compound is then reacted with the amine 1.6 to yield the hydroxyamine 3.4. The reaction is performed as described above for the preparation of the hydroxyamine 1.7. The hydroxyl substituent is then protected by conversion to the silyl ether 3.5, in which OTBD is tert. butyldimethylsilyloxy. The preparation of silyl ethers is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 77. The reaction is effected by treatment of the carbinol with tert. butylchlorodimethylsilane and a base such as imidazole, dimethylaminopyridine or 2,6-lutidine, in an organic solvent such as dichloromethane or dimethylformamide. Preferably, equimolar amounts of the carbinol, tert. butylchlorodimethylsilane and imidazole are reacted in dimethylformamide at ambient temperature to give the silyl ether 3.5. The benzyl ether is then removed to afford the carbinol 3.6. The removal of benzyl protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 49. The conversion is effected by means of catalytic hydrogenation over a palladium catalyst, with hydrogen or a hydrogen transfer agent, or by electrolytic reduction, by treatment with trimethylsilyl iodide, or by the use of a Lewis acid such as boron trifluoride or stannic chloride, or by oxidation with ferric chloride or ruthenium dioxide. Preferably, the benzyl ether is removed by reaction of the substrate with 5% palladium on carbon catalyst and ammonium formate in refluxing methanol, as described in Synthesis, 76, 1985. The resultant

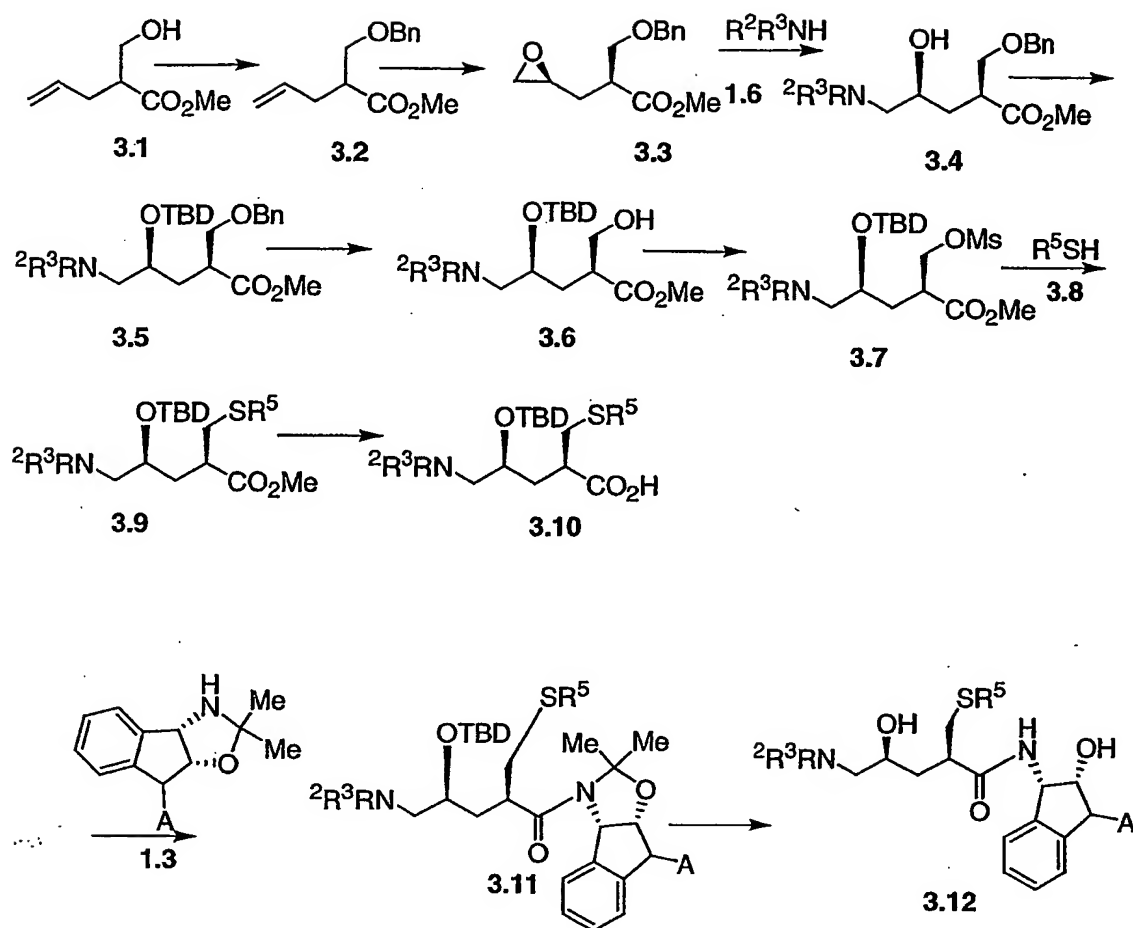
carbinol 3.6 is then converted into the mesylate ester 3.7 by reaction with one molar equivalent of methanesulfonyl chloride or anhydride, in an organic solvent such as dichloromethane, and in the presence of a base such as dimethylaminopyridine or diisopropylethylamine. The product 3.7 is then reacted with the thiol R^5SH , to prepare the thioether 3.9. The preparation

- 5 of thioethers by alkylation of thiols is described in Synthetic Organic Chemistry, by R. B. Wagner, H. D. Zook, Wiley, 1953, p. 787. The reaction is effected by treatment of the thiol with a base such as sodium hydroxide, potassium carbonate or diazabicyclononene, in a solvent such as ethanol or dioxan, in the presence of the mesylate 3.7, to afford the product 3.9. The methyl ester moiety present in the latter compound is then hydrolyzed to give the
- 10 carboxylic acid 3.10. The transformation is effected hydrolytically, for example by the use of an alkali metal hydroxide in an aqueous organic solvent, or enzymically, for example by the use of porcine liver esterase, as described in J. Am. Chem. Soc., 104, 7294, 1982. Preferably, the ester group is hydrolyzed by treatment of the ester 3.9 with one molar equivalent of lithium hydroxide in aqueous methanol at ambient temperature, to give the carboxylic acid
- 15 3.10. The latter compound is then reacted, as described above, with the aminoindanol acetone 1.3 to give the amide 3.11. Removal of the acetone group, as described above, with concomitant desilylation, then affords the hydroxyamide 3.12.

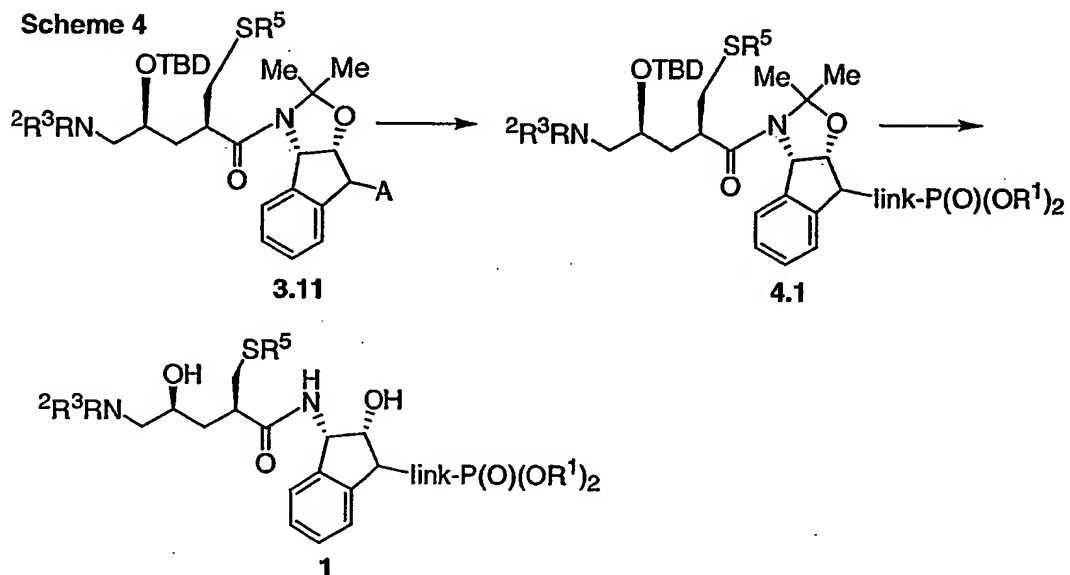
- The reactions shown in Scheme 3 illustrate the preparation of the compounds 3.12 in which A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 4
- 20 depicts the conversion of the compounds 3.11 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 1 in which X is sulfur. In this procedure, the compounds 3.11 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 4.1. Deprotection, by removal of the acetone protecting group, as described above, then affords the intermediate phosphonate esters 1 in which X is sulfur.

25

Scheme 3



Scheme 4

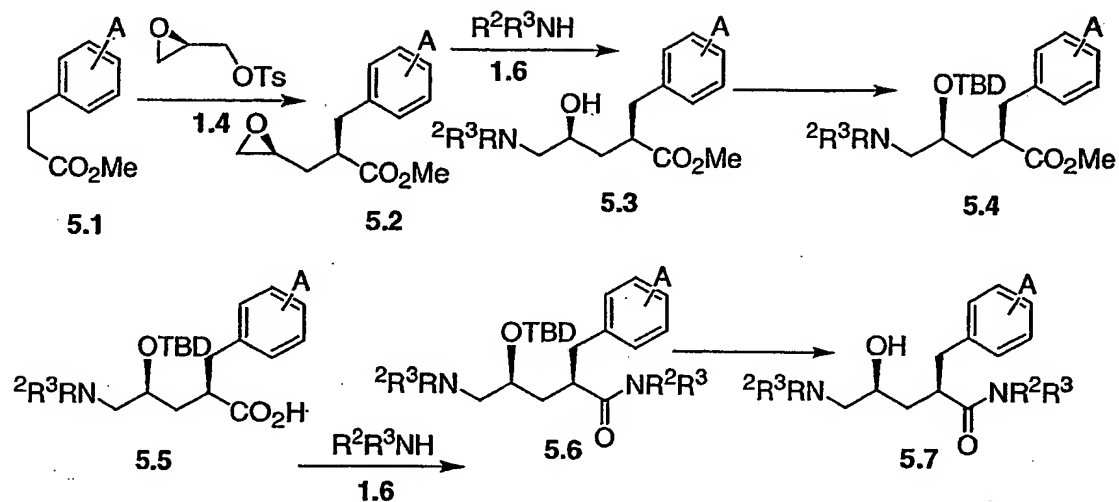


Preparation of the phosphonate ester intermediates 2 in which X is a direct bond.

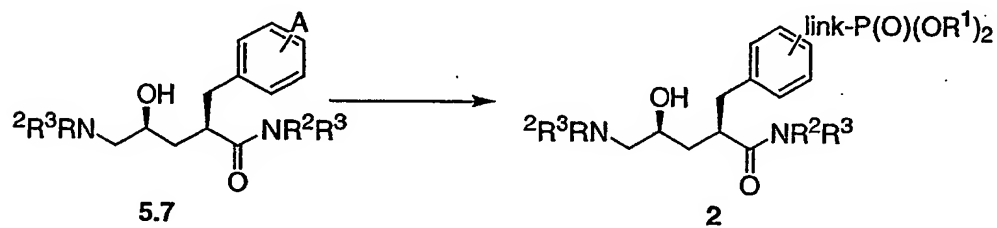
- 5 Schemes 5 and 6 illustrate the preparation of the phosphonate esters 2 in which X is a direct bond. As shown in Scheme 5, the substituted phenyl propionic ester 5.1, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br, is reacted with the glycidyl tosylate 1.4 to afford the alkylated product 5.2. The preparation of the phenylpropionic esters 5.1 is described below, (Schemes 138 - 143). The
- 10 reaction is performed as described above for the preparation of the oxirane 1.5. The product 5.2 is then reacted with the amine R²R³NH (1.6) to yield the hydroxyamine 5.3. The reaction is performed as described above for the preparation of the hydroxyamine 1.7. The secondary hydroxy group is then protected, for example by conversion to the tert. butyldimethyl silyl ether 5.4, using the conditions described above for the preparation of the silyl ether 3.5. The
- 15 methyl ester is then hydrolyzed to produce the carboxylic acid 5.5, using the conditions described above for the hydrolysis of the methyl ester 3.9. The carboxylic acid is then coupled with the amine 1.6 to give the amide 5.6. The reaction is effected under the conditions described above for the preparation of the amide 1.3. The product is desilylated, for example by treatment with 1M tetrabutyl ammonium fluoride in tetrahydrofuran, as described in J. Am.
- 20 Chem. Soc., 94, 6190, 1972, to give the carbinol 5.7.

- The reactions shown in Scheme 5 illustrate the preparation of the compounds 5.7 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br, as described herein. Scheme 6 depicts the conversion of the compounds 5.7 in which A is
- 25 [OH], [SH], [NH], Br, into the phosphonate esters 2 in which X is a direct bond. In this procedure, the compounds 5.7 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 2.

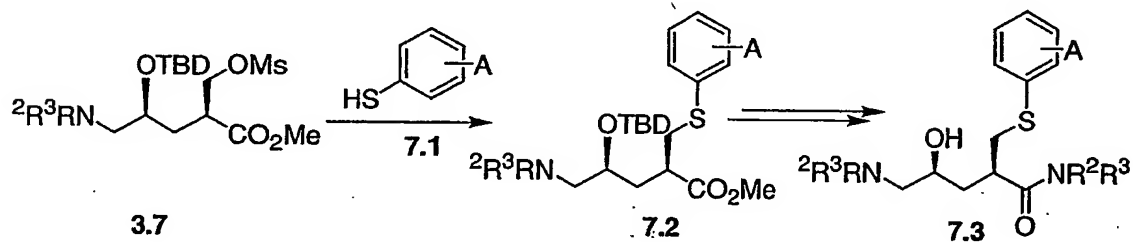
Scheme 5



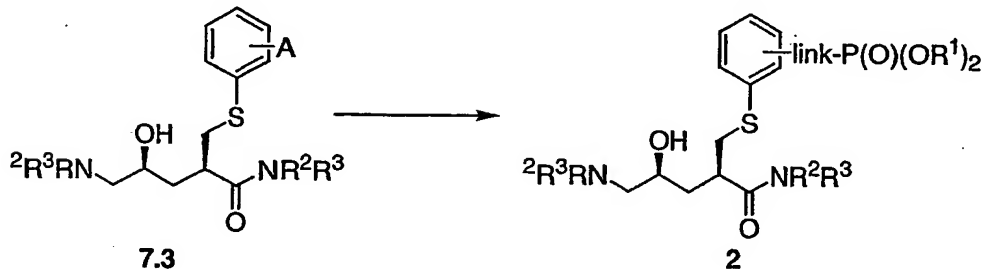
Scheme 6



Scheme 7



Scheme 8



Preparation of the phosphonate ester intermediates 2 in which X is sulfur.

Schemes 7 and 8 illustrate the preparation of the phosphonate esters 2 in which X is sulfur. As shown in Scheme 7, the mesylate 3.7 is reacted with the thiophenol 7.1, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br, to afford the thioether 7.2. The reaction is performed under the same conditions as described above for the preparation of the thioether 3.9. The preparation of the thiophenols 7.2 is described in Schemes 144 - 153. The product 7.2 is then transformed, using the sequence of reactions described above for the conversion of the ester 5.4 into the aminoamide 5.7, into the aminoamide 7.3.

The reactions shown in Scheme 7 illustrate the preparation of the compounds 7.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 8 depicts the conversion of the compounds 7.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 2 in which X is sulfur. In this procedure, the compounds 7.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 2.

Preparation of the phosphonate ester intermediates 3 in which X is a direct bond.

Schemes 9 and 10 illustrate the preparation of the phosphonate esters 3 in which X is a direct bond. As shown in Scheme 9, the methyl ester 9.1 is reacted, as described above, (Scheme 1) with the epoxide 1.4 to afford the alkylated ester 9.2. The product is then reacted with the amine 9.3, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor, to yield the hydroxyamine 9.4. The preparation of the tert. butylamine derivatives 9.3 is described below, (Schemes 154 - 158). The hydroxyamine is then transformed, using the sequence of reactions described above for the conversion of the aminoester 5.3 into the aminoamide 5.7, into the aminoamide 9.5.

The reactions shown in Scheme 9 illustrate the preparation of the compounds 9.5 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 10 depicts the conversion of the compounds 9.5 in which A is [OH], [SH], [NH],

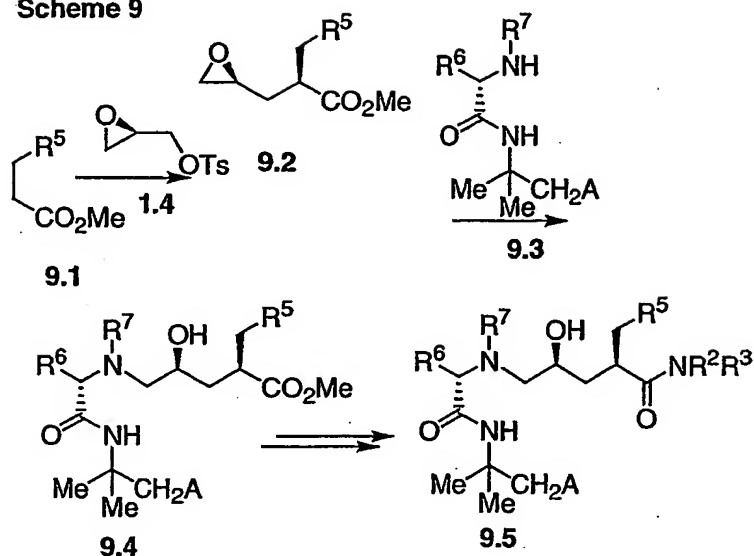
Br, into the phosphonate esters **3** in which X is a direct bond. In this procedure, the compounds **9.5** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **3**.

5 Preparation of the phosphonate ester intermediates **3 in which X is sulfur.**

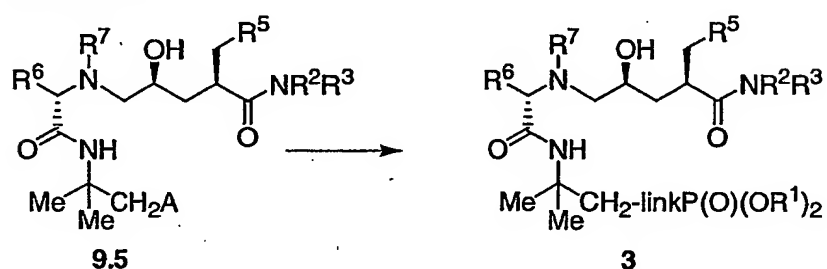
Schemes **11** and **12** illustrate the preparation of the phosphonate esters **3** in which X is sulfur. As shown in Scheme **11**, the benzyl-protected oxirane **3.3** is reacted, as described above, with the substituted tert. butylamine **9.3** to afford the hydroxyamine **11.1**. The product is then
10 converted, using the sequence of reactions shown in Scheme **5** for the conversion of the hydroxyamine **5.3** into the aminoamide **5.7**, into the aminoamide **11.2**.

The reactions shown in Scheme **11** illustrate the preparation of the compounds **11.2** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH],
15 [NH], Br. Scheme **12** depicts the conversion of the compounds **11.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **3** in which X is sulfur. In this procedure, the compounds **11.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **3**.

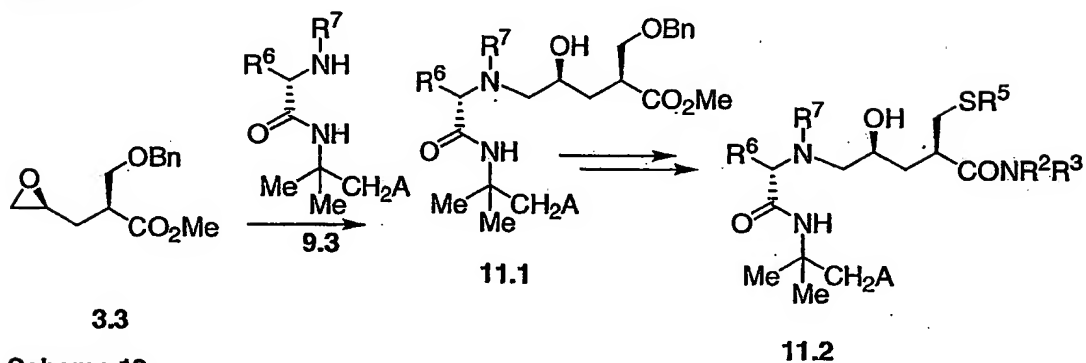
Scheme 9



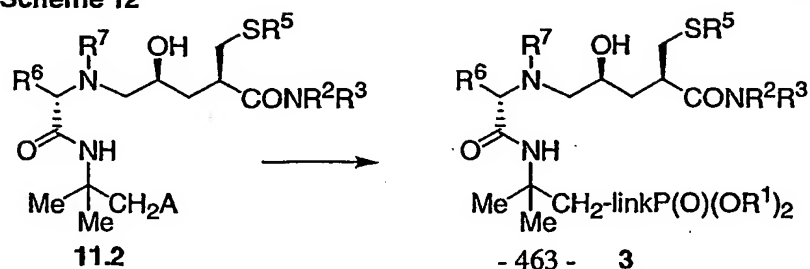
Scheme 10



Scheme 11



Scheme 12



Preparation of the phosphonate ester intermediates 4 in which X is a direct bond.

Schemes 13 and 14 illustrate the preparation of the phosphonate esters 4 in which X is a direct bond. As shown in Scheme 13, the oxirane 9.2 is reacted, as described in Scheme 1, with the pyridyl piperazine derivative 13.1 to produce the hydroxyamine 13.2. The preparation of the pyridyl piperazine derivatives 13.1 is described in Schemes 159 – 164. The product is then transformed, as described previously, (Scheme 5) into the amide 13.3.

The reactions shown in Scheme 13 illustrate the preparation of the compounds 13.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 12 depicts the conversion of the compounds 13.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 4 in which X is a direct bond. In this procedure, the compounds 13.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 4.

Preparation of the phosphonate ester intermediates 4 in which X is sulfur.

Schemes 15 and 16 illustrate the preparation of the phosphonate esters 4 in which X is sulfur. As shown in Scheme 15, the benzyl-protected oxirane 3.3 is reacted, as described above, with the pyridyl piperazine derivative 13.1 to afford the hydroxyamine 15.1. The product is then converted, as described above (Scheme 5) into the aminoamide 15.2.

The reactions shown in Scheme 15 illustrate the preparation of the compounds 15.2 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 16 depicts the conversion of the compounds 15.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 4 in which X is sulfur. In this procedure, the compounds 15.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 4.

Preparation of the phosphonate ester intermediates 5 in which X is a direct bond.

Schemes 17 and 18 illustrate the preparation of the phosphonate esters 5 in which X is a direct bond. As shown in Scheme 17, the oxirane 9.2 is reacted, as described in Scheme 1, with the decahydroisoquinoline derivative 17.1 to produce the hydroxyamine 17.2. The preparation of the decahydroisoquinoline derivatives 17.1 is described in Schemes 192 – 197. The product is then transformed, as described previously, (Scheme 3) into the amide 17.3.

- 10 The reactions shown in Scheme 17 illustrate the preparation of the compounds 17.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 18 depicts the conversion of the compounds 17.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 5 in which X is a direct bond. In this procedure, the compounds 17.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 5.

Preparation of the phosphonate ester intermediates 5 in which X is sulfur.

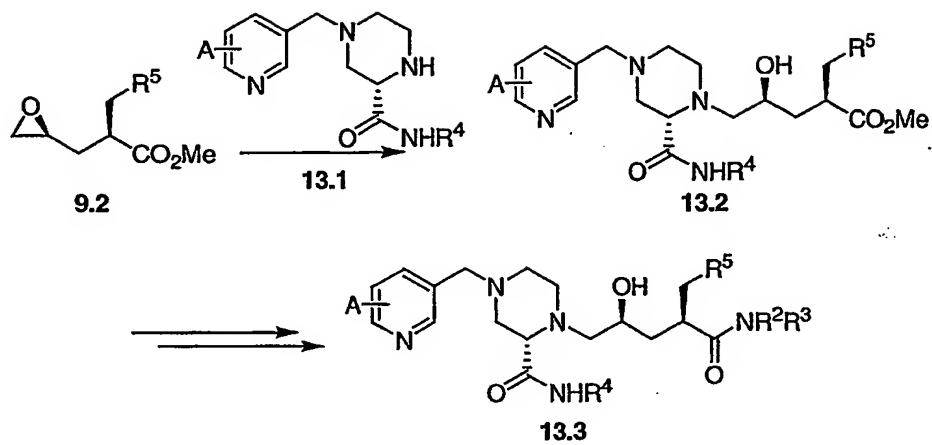
Schemes 19 and 20 illustrate the preparation of the phosphonate esters 5 in which X is sulfur.

- 20 As shown in Scheme 19, the benzyl-protected oxirane 3.3 is reacted, as described above, with the decahydroisoquinoline derivative 17.1 to afford the hydroxyamine 19.1. The product is then converted, as described above (Scheme 5) into the aminoamide 19.2.

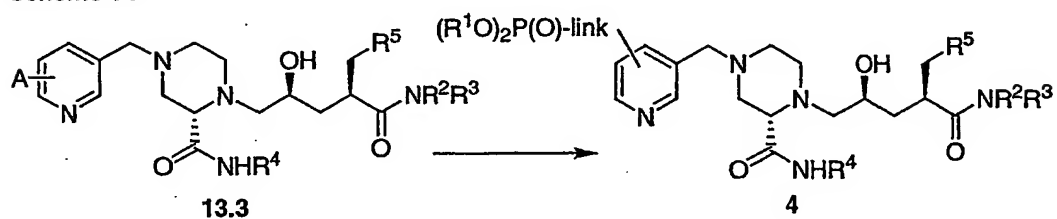
- 25 The reactions shown in Scheme 19 illustrate the preparation of the compounds 19.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 20 depicts the conversion of the compounds 19.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 5 in which X is sulfur. In this procedure, the compounds 19.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 5.

30

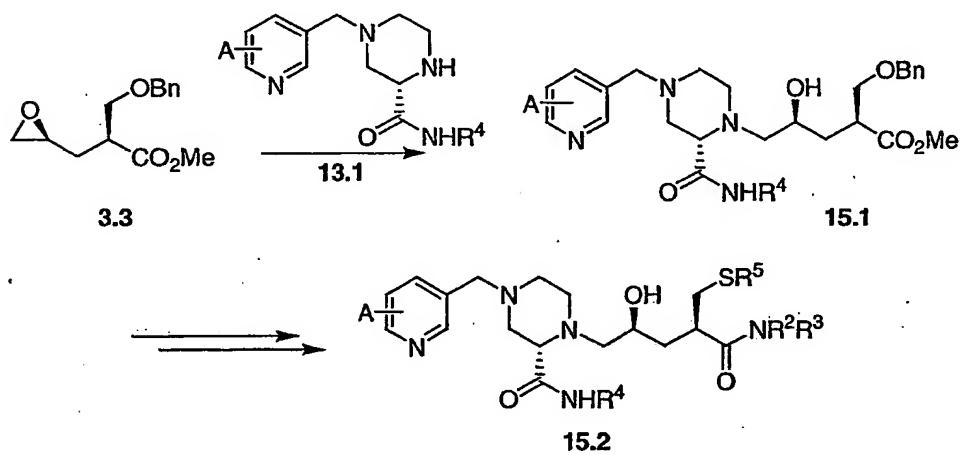
Scheme 13



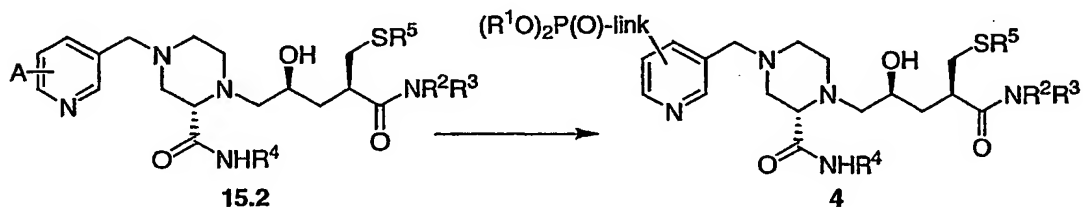
Scheme 14



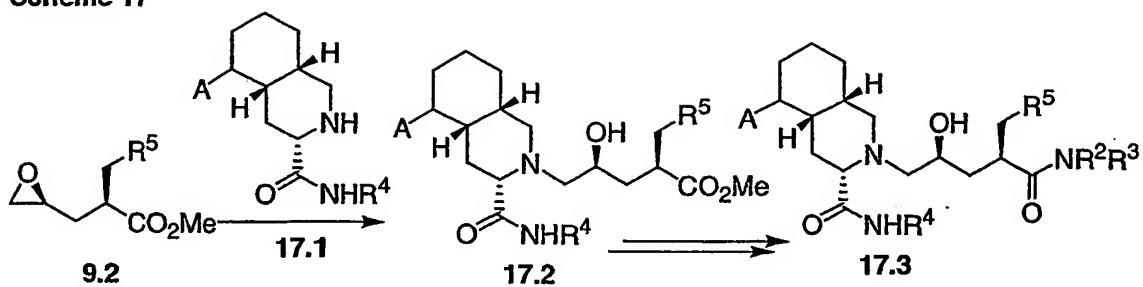
Scheme 15



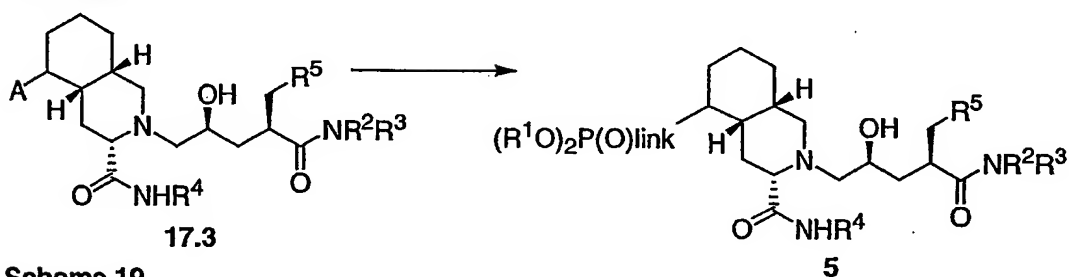
Scheme 16



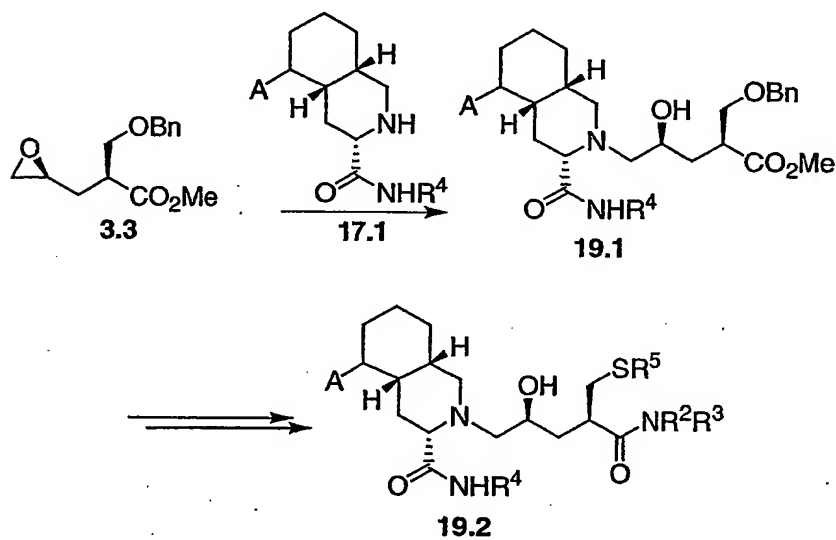
Scheme 17



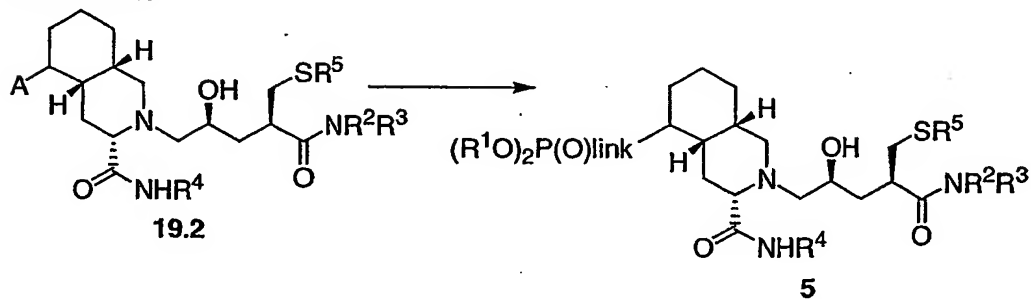
Scheme 18



Scheme 19



Scheme 20



Preparation of the phosphonate ester intermediates 6 in which X is a direct bond.

Schemes 21 and 22 illustrate the preparation of the phosphonate esters 6 in which X is a direct bond. As shown in Scheme 21, the glycidyl tosylate 1.4 is reacted, as described in Scheme 5, with the anion of the dimethoxyphenyl propionic ester 21.1 to afford the alkylated product 21.2. The preparation of the dimethoxyphenyl propionic ester derivatives 21.1 is described in Scheme 186. The product is then transformed, as described previously, (Scheme 5) into the amide 21.3.

10 The reactions shown in Scheme 21 illustrate the preparation of the compounds 21.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 22 depicts the conversion of the compounds 21.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 6 in which X is a direct bond. In this procedure, the compounds 21.3 are converted, using the procedures described below, Schemes 133 - 197,
15 into the compounds 6.

Preparation of the phosphonate ester intermediates 6 in which X is sulfur.

Schemes 23 and 24 illustrate the preparation of the phosphonate esters 6 in which X is sulfur.
20 As shown in Scheme 23, the mesylate 3.7 is reacted, as described in Scheme 3, with the dimethoxyphenyl mercaptan 23.1 to yield the thioether 23.2. The preparation of the substituted thiols 23.1 is described below in Schemes 170 - 173. The product is then converted, as described above (Scheme 5) into the aminoamide 23.3.

25 The reactions shown in Scheme 23 illustrate the preparation of the compounds 23.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 24 depicts the conversion of the compounds 23.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 6 in which X is sulfur. In this procedure, the compounds 23.3 are converted, using the procedures described below, Schemes 133 - 197,
30 into the compounds 6.

Preparation of the phosphonate ester intermediates 7 in which X is a direct bond.

Schemes 25 and 26 illustrate the preparation of the phosphonate esters 7 in which X is a direct bond. As shown in Scheme 25, the oxirane 9.2 is reacted, as described above (Scheme 1) with the amine 1.6 to afford the hydroxyamine 25.1. The product is then converted into the silyl ether 25.2, using the procedures described in Scheme 3. The methyl ester is then hydrolyzed to give the carboxylic acid 25.3, and this compound is then coupled with the tert. butylamine derivative 25.4, using the procedures described in Scheme 1, to yield the amide 25.5. The preparation of the tert. butylamine derivatives 25.4 is described in Schemes 154 – 157. Desilylation then produces the hydroxyamide 25.6.

The reactions shown in Scheme 25 illustrate the preparation of the compounds 25.6 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 26 depicts the conversion of the compounds 25.6 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 7 in which X is a direct bond. In this procedure, the compounds 25.6 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 7.

Preparation of the phosphonate ester intermediates 7 in which X is sulfur.

Schemes 27 and 28 illustrate the preparation of the phosphonate esters 7 in which X is sulfur. As shown in Scheme 27, the carboxylic acid 3.10 is coupled, as described in Scheme 3, with the tert. butylamine derivative 25.4 to yield the amide product 27.1. The product is then desilylated, as described above, to afford the amide 27.2.

The reactions shown in Scheme 27 illustrate the preparation of the compounds 27.2 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 28 depicts the conversion of the compounds 27.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 7 in which X is sulfur. In this procedure, the compounds 27.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 7.

Preparation of the phosphonate ester intermediates 8 in which X is a direct bond.

Schemes 29 and 30 illustrate the preparation of the phosphonate esters 8 in which X is a direct bond. As shown in Scheme 29, the silylated carboxylic acid 25.3 is coupled, as described above, (Scheme 1) with the amine 29.1 to afford the amide 29.2 which upon desilylation produces the hydroxyamide 29.3. The preparation of the ethanolamine derivatives 29.1 is described in Schemes 174 – 178.

10 The reactions shown in Scheme 29 illustrate the preparation of the compounds 29.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 30 depicts the conversion of the compounds 29.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 8 in which X is a direct bond. In this procedure, the compounds 29.3 are converted, using the procedures described below, Schemes 133 - 197,
15 into the compounds 8.

Preparation of the phosphonate ester intermediates 8 in which X is sulfur.

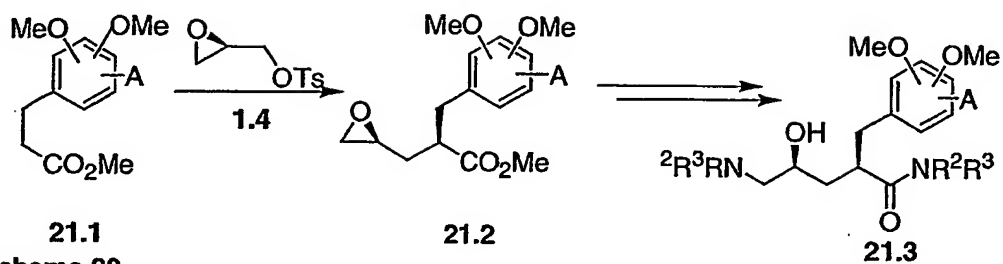
Schemes 31 and 32 illustrate the preparation of the phosphonate esters 8 in which X is sulfur. As shown in Scheme 31, the carboxylic acid 3.10 is coupled, as described previously, with the ethanolamine derivative 29.1 to yield the amide; the product is then desilylated, as described above, to afford the hydroxyamide 31.1.

25 The reactions shown in Scheme 31 illustrate the preparation of the compounds 31.1 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 32 depicts the conversion of the compounds 31.1 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 8 in which X is sulfur. In this procedure, the compounds 31.1 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 8.

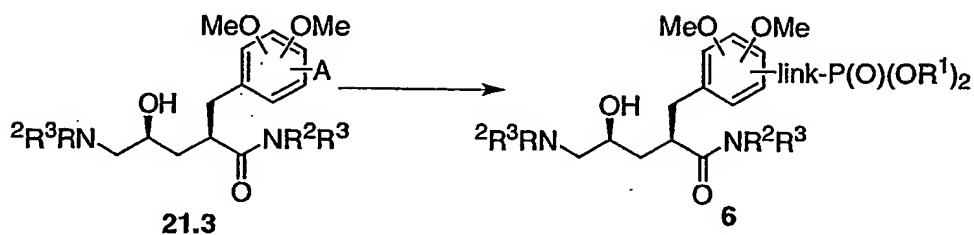
Preparation of the phosphonate ester intermediates 9 in which X is a direct bond.

- Schemes 33 and 34 illustrate the preparation of the phosphonate esters 9 in which X is a direct bond. As shown in Scheme 33, the silylated carboxylic acid 25.3 is coupled, as described above, (Scheme 1) with the chroman amine 33.1 to afford the corresponding amide, which upon desilylation produces the hydroxyamide 33.2. The preparation of the chroman amines 33.1 is described in Schemes 179 – 181a.
- 10 The reactions shown in Scheme 33 illustrate the preparation of the compounds 33.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 34 depicts the conversion of the compounds 33.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 9 in which X is a direct bond. In this procedure, the compounds 33.2 are converted, using the procedures described below, Schemes 133 - 197,
- 15 into the compounds 9.

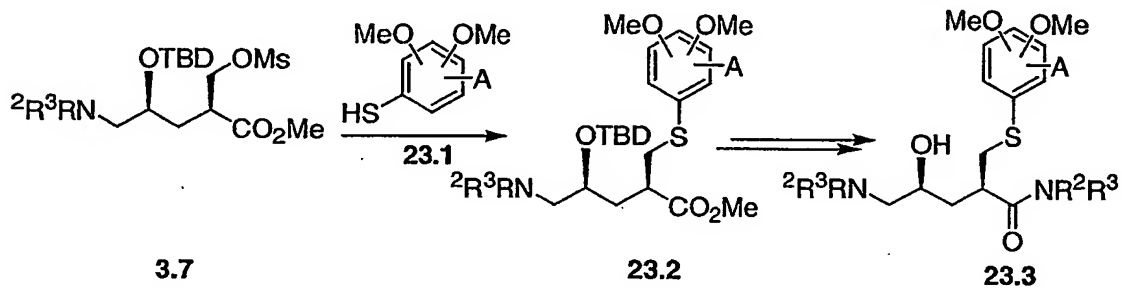
Scheme 21



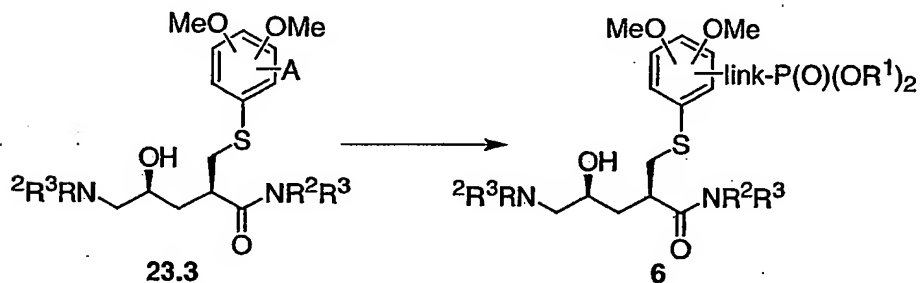
Scheme 22



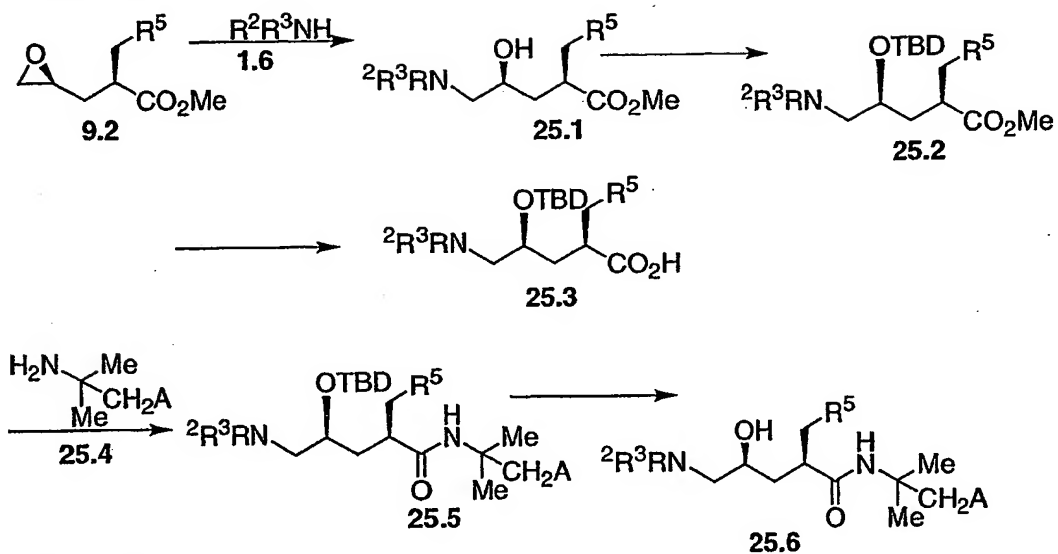
Scheme 23



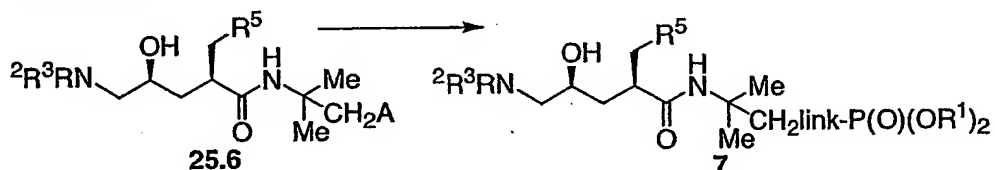
Scheme 24



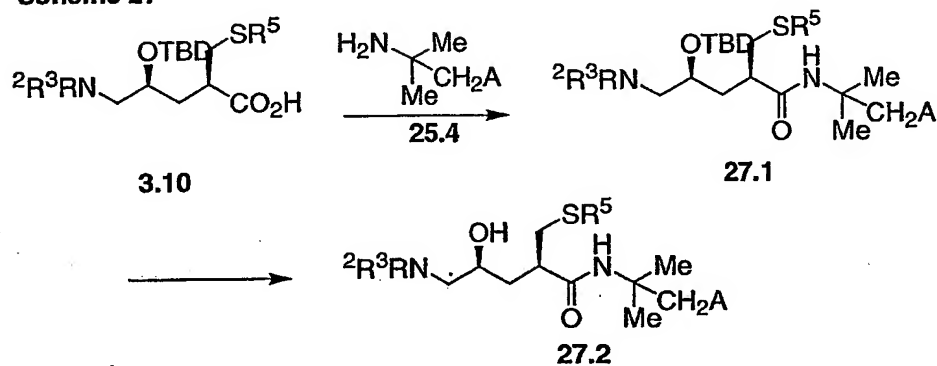
Scheme 25



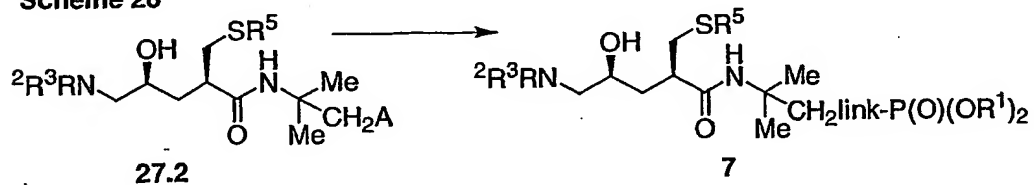
Scheme 26



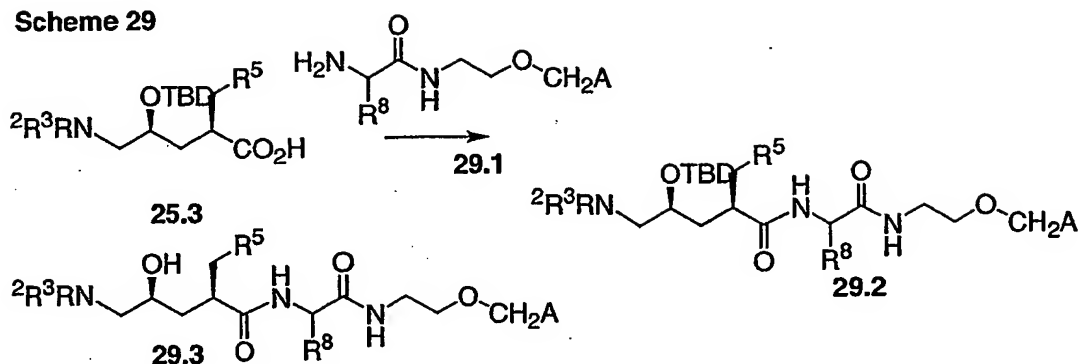
Scheme 27



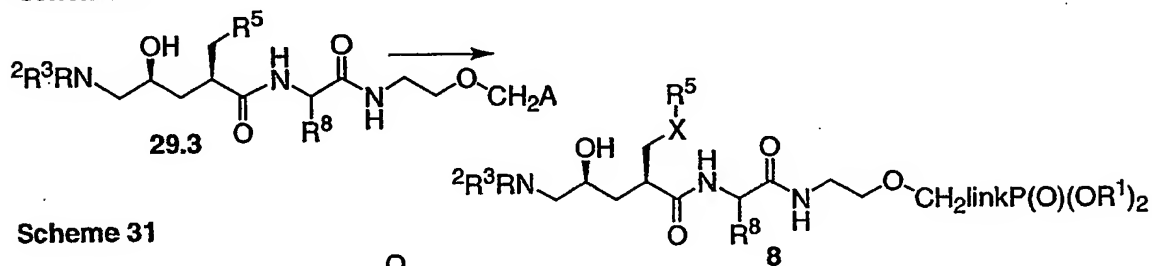
Scheme 28



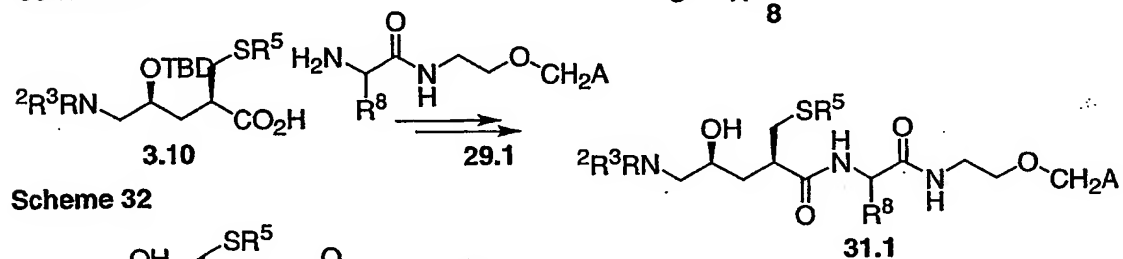
Scheme 29



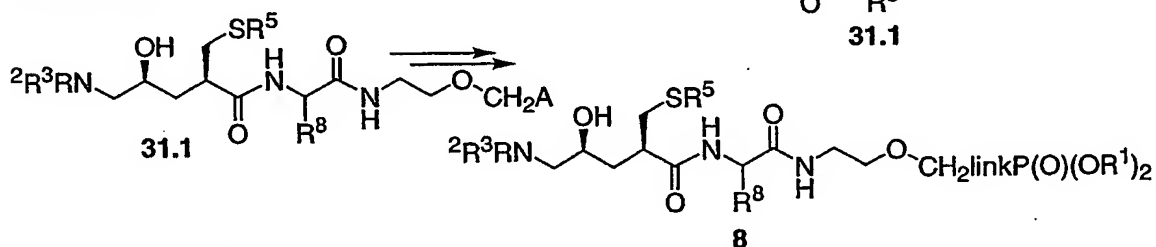
Scheme 30



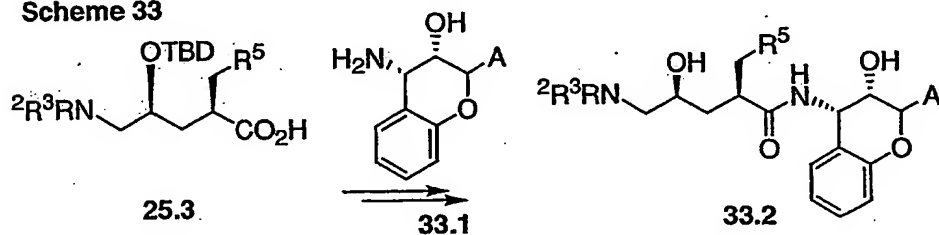
Scheme 31



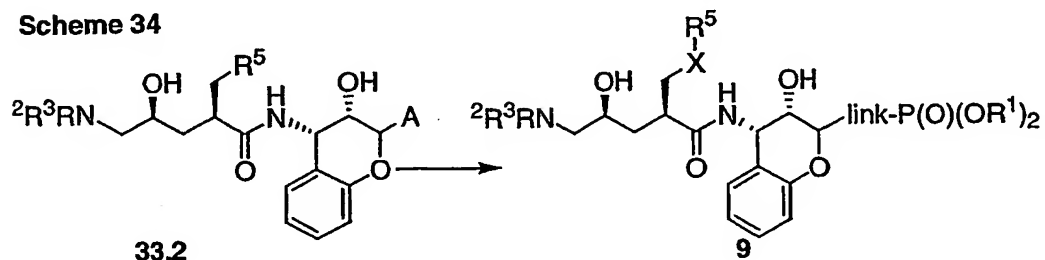
Scheme 32



Scheme 33



Scheme 34



Preparation of the phosphonate ester intermediates 9 in which X is sulfur.

- 5 Schemes 35 and 36 illustrate the preparation of the phosphonate esters 9 in which X is sulfur. As shown in Scheme 35, the carboxylic acid 3.10 is coupled, as described previously, with the chroman amine 33.1 to yield the amide; the product is then desilylated, as described above, to afford the amide 35.1.
- 10 The reactions shown in Scheme 35 illustrate the preparation of the compounds 35.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 36 depicts the conversion of the compounds 35.1 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 9 in which X is sulfur. In this procedure, the compounds 35.1 are converted, using the procedures described below, Schemes 133 - 197,
- 15 into the compounds 9.

Preparation of the phosphonate ester intermediates 10 in which X is a direct bond.

- 20 Schemes 37 and 38 illustrate the preparation of the phosphonate esters 10 in which X is a direct bond. As shown in Scheme 37, the silylated carboxylic acid 25.3 is coupled, as described above, (Scheme 1) with the phenylalanine derivative 37.1 to afford the corresponding amide, which upon desilylation produces the hydroxyamide 37.2. The preparation of the phenylalanine derivatives 37.1 is described in Schemes 182 - 185.
- 25 The reactions shown in Scheme 37 illustrate the preparation of the compounds 37.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 38 depicts the conversion of the compounds 37.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 10 in which X is a direct bond. In this procedure, the compounds 37.2 are converted, using the procedures described below, Schemes 133 - 197,
- 30 into the compounds 10.

Preparation of the phosphonate ester intermediates 10 in which X is sulfur.

Schemes 39 and 40 illustrate the preparation of the phosphonate esters 10 in which X is sulfur.

- 5 As shown in Scheme 39, the carboxylic acid 3.10 is coupled, as described previously, with the phenylalanine derivative 37.1 to yield the corresponding amide; the product is then desilylated, as described above, to afford the amide 39.1.

- 10 The reactions shown in Scheme 39 illustrate the preparation of the compounds 39.1 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 40 depicts the conversion of the compounds 39.1 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 10 in which X is sulfur. In this procedure, the compounds 39.1 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 10.

15

Preparation of the phosphonate ester intermediates 11 in which X is a direct bond.

- Schemes 41 and 42 illustrate the preparation of the phosphonate esters 11 in which X is a direct bond. As shown in Scheme 41, the silylated carboxylic acid 25.3 is coupled, as described above, (Scheme 1) with the decahydroisoquinoline carboxamide 41.1, prepared as described in Scheme 158, to afford the corresponding amide, which upon desilylation produces the hydroxyamide 41.2.

- 25 The reactions shown in Scheme 41 illustrate the preparation of the compounds 41.2 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 42 depicts the conversion of the compounds 41.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 11 in which X is a direct bond. In this procedure, the compounds 41.2 are converted, using the procedures described below, Schemes 133 - 197, into the compound

Preparation of the phosphonate ester intermediates 11 in which X is sulfur.

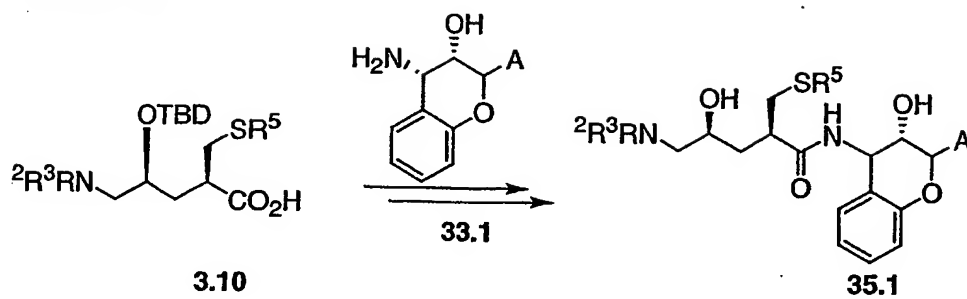
Schemes 43 and 44 illustrate the preparation of the phosphonate esters 11 in which X is sulfur.

- 5 As shown in Scheme 43, the carboxylic acid 3.10 is coupled, as described previously, with the decahydroisoquinoline carboxamide 41.1 to yield the corresponding amide; the product is then desilylated, as described above, to afford the amide 43.1.

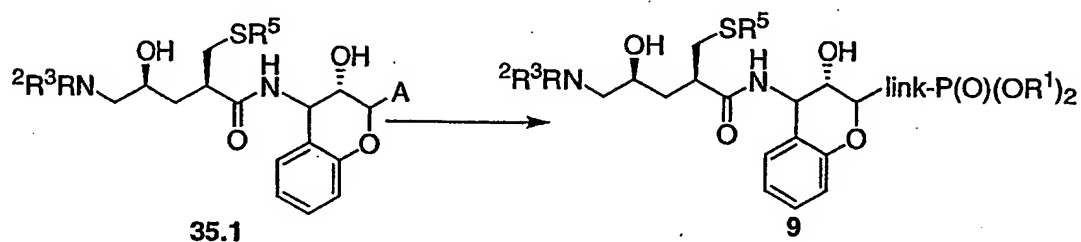
- 10 The reactions shown in Scheme 43 illustrate the preparation of the compounds 43.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 44 depicts the conversion of the compounds 43.1 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 11 in which X is sulfur. In this procedure, the compounds 43.1 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 11.

15

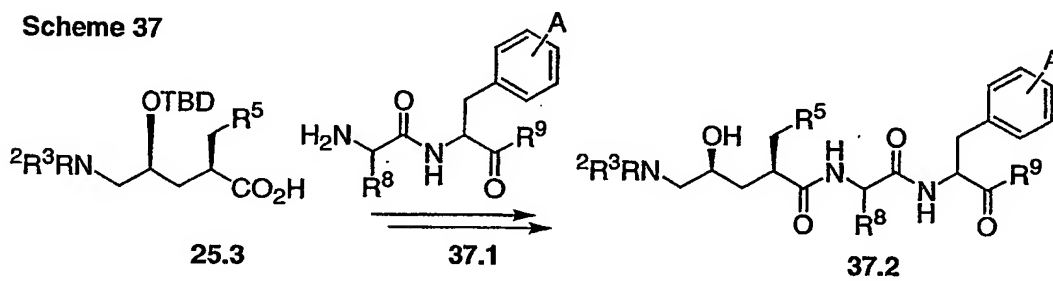
Scheme 35



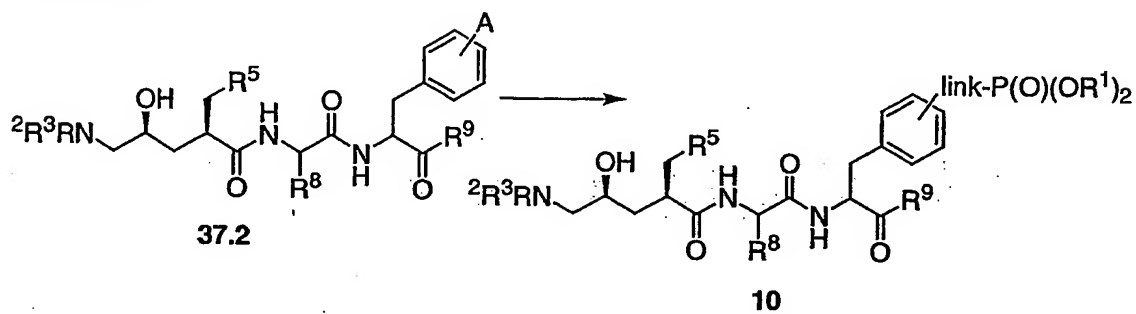
Scheme 36



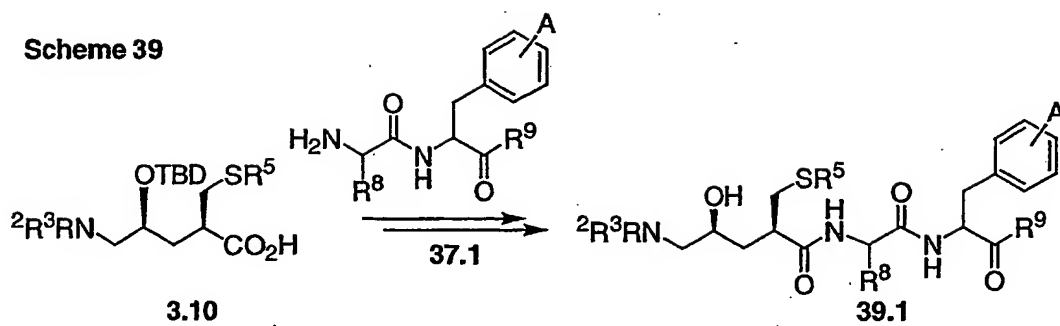
Scheme 37



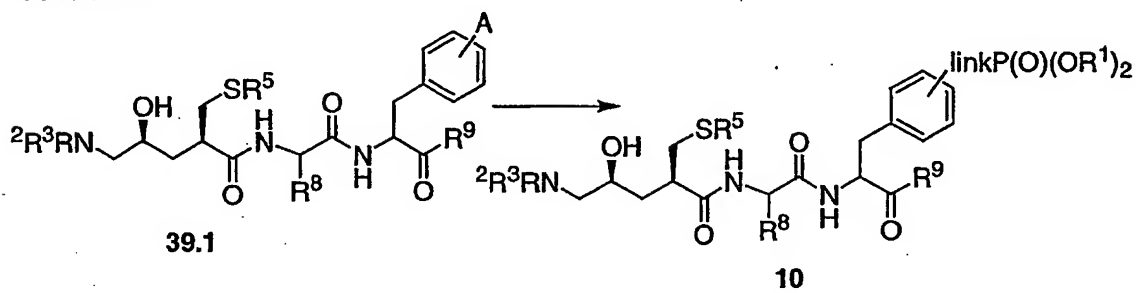
Scheme 38



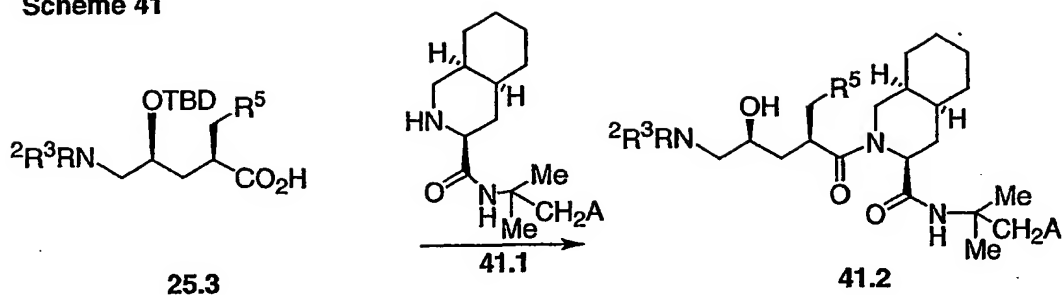
Scheme 39



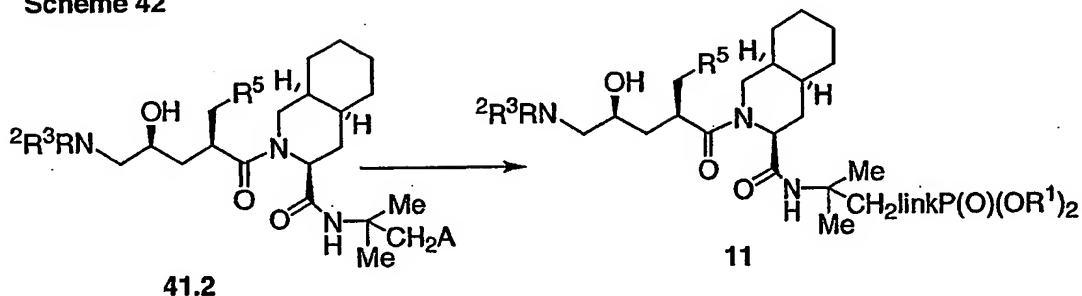
Scheme 40



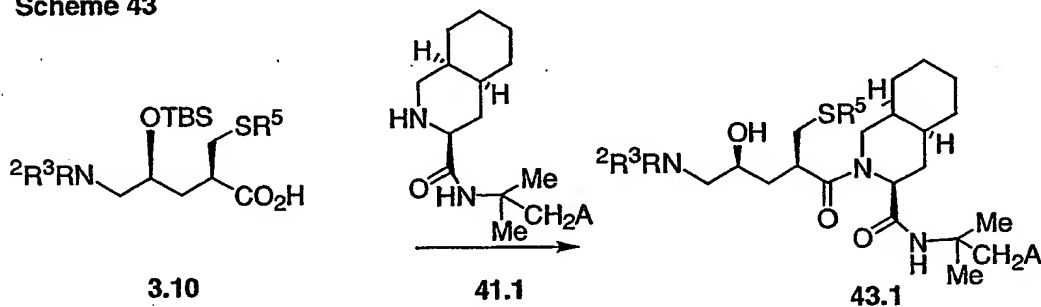
Scheme 41



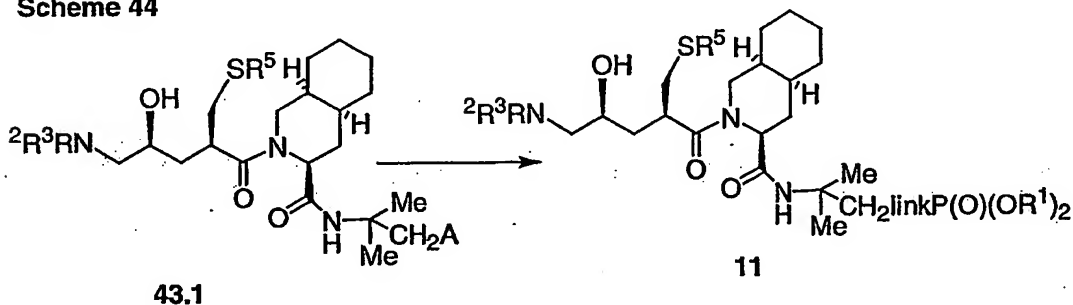
Scheme 42



Scheme 43



Scheme 44



Preparation of the phosphonate ester intermediates 12 in which X is a direct bond.

Schemes 45 and 46 illustrate the preparation of the phosphonate esters 12 in which X is a direct bond. As shown in Scheme 45, the silylated carboxylic acid 25.3 is coupled, as described above, (Scheme 1) with the decahydroisoquinoline derivative 45.1 to afford the

corresponding amide, which upon desilylation produces the hydroxyamide 45.2. The preparation of the decahydroisoquinoline derivatives 45.1 is described in Schemes 192 – 197.

The reactions shown in Scheme 45 illustrate the preparation of the compounds 45.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 46 depicts the conversion of the compounds 45.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 12 in which X is a direct bond. In this procedure, the compounds 45.2 are converted, using the procedures described below, Schemes 133 – 197, into the compounds 12.

Preparation of the phosphonate ester intermediates 12 in which X is sulfur.

Schemes 47 and 48 illustrate the preparation of the phosphonate esters 12 in which X is sulfur. As shown in Scheme 47, the carboxylic acid 3.10 is coupled, as described previously, with the decahydroisoquinoline derivative 45.1 to yield the corresponding amide; the product is then desilylated, as described above, to afford the amide 47.1.

The reactions shown in Scheme 47 illustrate the preparation of the compounds 47.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 48 depicts the conversion of the compounds 47.1 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 12 in which X is sulfur. In this procedure, the compounds 47.1 are converted, using the procedures described below, Schemes 133 – 197, into the compounds 12.

Preparation of the phosphonate ester intermediates 13 in which X and X' are direct bonds.

Schemes 49 and 50 illustrate the preparation of the phosphonate esters 12 in which X and X' are direct bonds. As shown in Scheme 49, a BOC-protected aminoacid 49.1 is converted into the corresponding aldehyde 49.2. A number of methods are known for the conversion of carboxylic acids and derivatives into the corresponding aldehydes, for example as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 619-627. The

conversion is effected by direct reduction of the carboxylic acid, for example employing diisobutyl aluminum hydride, as described in J. Gen. Chem. USSR., 34, 1021, 1964, or alkyl borane reagents, for example as described in J. Org. Chem., 37, 2942, 1972. Alternatively, the carboxylic acid is converted into an amide, such as the N-methoxy N-methyl amide, and the latter compound is reduced with lithium aluminum hydride, for example as described in J. Med. Chem., 1994, 37, 2918, to afford the aldehyde. Alternatively, the carboxylic acid is reduced to the corresponding carbinol which is then oxidized to the aldehyde. The reduction of carboxylic acids to carbinols is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 548ff. The reduction reaction is performed by the use of reducing agents such as borane, as described in J. Am. Chem. Soc., 92, 1637, 1970, or by lithium aluminum hydride, as described in Org. Reac., 6, 649, 1951. The resultant carbinol is then converted into the aldehyde by means of an oxidation reaction. The oxidation of a carbinol to the corresponding aldehyde is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. The conversion is effected by the use of oxidizing agents such as pyridinium chlorochromate, as described in J. Org. Chem., 50, 262, 1985, or silver carbonate, as described in Compt. Rend. Ser. C., 267, 900, 1968, or dimethyl sulfoxide/acetic anhydride, as described in J. Am. Chem. Soc., 87, 4214, 1965. Preferably, the procedure described in EP 708085 is employed. The carboxylic acid 49.1 is first reacted with equimolar amounts of isobutyl chloroformate and triethylamine in tetrahydrofuran, to afford a mixed anhydride which is then reduced by treatment with sodium borohydride in aqueous tetrahydrofuran at ambient temperature to afford the carbinol 49.2. The carbinol is then oxidized to the aldehyde 49.3 by reaction with oxalyl chloride and dimethylsulfoxide in dichloromethane at -60°C, as described in EP708085. To transform the aldehyde into the hydroxyester 49.5, ethyl 3-iodopropionate 49.4 is reacted first with a zinc-copper couple, prepared as described in Org. Syn. Coll. Vol. 5, 855, 1973, and the product is then reacted with trichlorotitanium isopropoxide, as described in EP 708085. The resultant reagent is then treated with the aldehyde 49.3 in dichloromethane at -20°C to yield the hydroxyester 49.5. The hydroxyester is then cyclized to the lactone 49.6 by treatment with acetic acid in toluene at 100°C, as described in EP 708085. A number of alternative preparations of the lactone 49.6 are known, for example as described in J. Org. Chem., 1985, 50, 4615, J. Org. Chem., 1995, 60, 7927 and J. Org. Chem., 1991, 56, 6500. The lactone 49.6 is then reacted with a substituted benzyl iodide 49.7 to afford the alkylated product 49.8.

The preparation of the benzyl halides **49.7** is described below, (Schemes **165 – 169**). The alkylation reaction is performed in an aprotic organic solvent such as dimethylformamide or tetrahydrofuran, in the presence of a strong base such as sodium hydride or lithium hexamethyl disilylazide. Preferably, the lactone is first reacted with lithium bis(trimethylsilyl)amide in a mixture of tetrahydrofuran and 1,3-dimethyltetrahydropyrimidinone, and then ethyl 3-iodopropionate is added, as described in EP 708085, to prepare the alkylated lactone **49.8**. The lactone is then converted into the corresponding hydroxyacid **49.9** by alkaline hydrolysis, for example by treatment with lithium hydroxide in aqueous dimethoxyethane, as described in EP 708085. The hydroxyacid is then converted into the tert. butyldimethylsilyl ether **49.10**, by reaction with excess chloro tert. butyldimethylsilane and imidazole in dimethylformamide, followed by alkaline hydrolysis, employing potassium carbonate in aqueous methanolic tetrahydrofuran, as described in EP 708085, to yield the silyl ether **49.10**. The carboxylic acid is then coupled, as described above (Scheme 5) with the amine R^2R^3NH to afford the amide product **49.11**. The BOC protecting group is then removed to give the free amine **49.12**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC protecting group is removed by treatment of the substrate with 3M hydrogen chloride in ethyl acetate, as described in J. Org. Chem., 43, 2285, 1978, a procedure which also removes the silyl protecting group to afford the hydroxy amine **49.12**. The latter compound is then coupled with the carboxylic acid $R^{10}COOH$, or a functional equivalent thereof, to give the amide or carbamate product **49.13**. The preparation of amides by the reaction between amines and amides is described above (Scheme 1).

Compounds in which the group R^{10} is alkoxy are carbamates; the preparation of carbamates is described below (Scheme **198**)

The reactions shown in Scheme **49** illustrate the preparation of the compounds **49.13** in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **50** depicts the conversion of the compounds **49.13** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **13** in which X and X' are direct bonds. In this procedure, the compounds **49.13** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **13**.

Preparation of the phosphonate ester intermediates 13 in which X is a direct bond and X' is sulfur.

- 5 Schemes 51 and 52 illustrate the preparation of the phosphonate esters 13 in which X is a direct bond and X' is sulfur. In this procedure, BOC serine methyl ester mesylate, 51.1, the preparation of which is described in Synlett., 1997, 169, is reacted with the thiol 51.2, employing the conditions described in Scheme 3, to prepare the thioether 51.3. The methyl ester group is then transformed into the corresponding aldehyde 51.4. The reduction of esters
10 to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 621. The conversion is effected by treatment with diisobutyl aluminum hydride, sodium aluminum hydride, lithium tri-tertiary butoxy aluminum hydride and the like. Preferably, the ester 51.3 is reduced to the aldehyde 51.4 by reaction with the stoichiometric amount of diisobutyl aluminum hydride in toluene at -80°C, as described in
15 Syn., 617, 1975. The aldehyde is then transformed into the diamide 51.5, using the sequence of reactions and reaction conditions described above (Scheme 49) for the conversion of the aldehyde 49.3 into the diamide 49.13.

- The reactions shown in Scheme 51 illustrate the preparation of the compounds 51.5 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH],
20 [NH], Br. Scheme 52 depicts the conversion of the compounds 51.5 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 13 in which X is a direct bond and X' is sulfur. In this procedure, the compounds 51.5 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 13.

- 25 **Preparation of the phosphonate ester intermediates 13 in which X and X' are sulfur.**

- Schemes 53, 54 and 55 illustrate the preparation of the phosphonate esters 13 in which X and X' are sulfur. As shown in Scheme 53, the aldehyde 51.4 is reacted with the dianion of N-methylmethacrylamide 53.1 to form the hydroxyamide 53.2. The dianion is generated by
30 treatment of N-methylmethacrylamide with two equivalents of an alkyl lithium, for example n-butyllithium, in an organic solvent such as tetrahydrofuran or dimethoxyethane, as described in J. Org. Chem., 1986, 51, 3921. The dianion is then reacted with the aldehyde in the presence

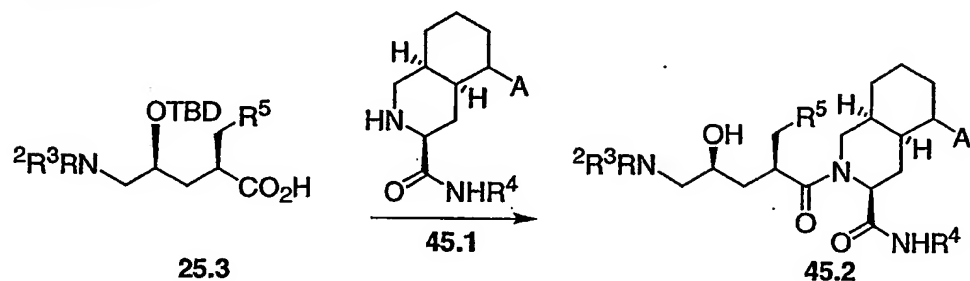
of chlorotitanium triisopropoxide, to afford the olefinic amide 53.2. The product is cyclized to produce the methylene lactone 53.3 by heating in an inert solvent such as xylene, at reflux temperature, as described in J. Org. Chem., 1986, 51, 3921. The methylene lactone is then reacted with the thiol 53.4 to yield the thioether 53.5. The preparation of the thiols 53.4 is
5 described below, (Schemes 170 – 173). The addition of thiols to methylene lactones analogous to the compound 53.3 is described in J. Org. Chem., 1986, 51, 3921. Equimolar amounts of the reactants are combined in an alcoholic solvent such as methanol at about 60°C, in the presence of a tertiary base such as triethylamine, to give the addition product 53.5. The latter compound is then subjected to basic hydrolysis, for example by reaction with lithium
10 hydroxide, as described above, (Scheme 49) to produce the hydroxyacid 53.6. The product is silylated, as described in Scheme 49, to give the silylated carbinol 53.7, and the product is then converted, as described in Scheme 49, into the diamide 53.8.

Scheme 54 illustrates an alternative method for the preparation of the diamides 53.8. In this
15 procedure, the anion of the lactone 54.1, obtained as an intermediate in the conversion of the aldehyde 51.4 into the diamide 51.5, (Scheme 51) is reacted with formaldehyde or a functional equivalent thereof, to afford the hydroxymethyl compound 54.2. The generation of the anion of lactones analogous to 54.1, and alkylation thereof, is described above in Scheme 49. Preferably, the anion is prepared by reaction of the lactone, in a solvent mixture composed of
20 tetrahydrofuran and 1,3-dimethyltetrahydropyrimidinone, with lithium bis(trimethylsilyl)amide, as described in EP 708085, and formaldehyde, generated by pyrolysis of paraformaldehyde, is then introduced in an inert gas stream. The hydroxymethyl product is then converted into the corresponding mesylate 54.3, by reaction with methanesulfonyl chloride in dichloromethane containing a tertiary base such as triethylamine or dimethylaminopyridine, and the mesylate is
25 then reacted with the thiol reagent 53.4, using the procedure described above for the preparation of the thioether 51.3, to yield the thioether 53.5. The product is then transformed, as described above, into the diamide 53.8.

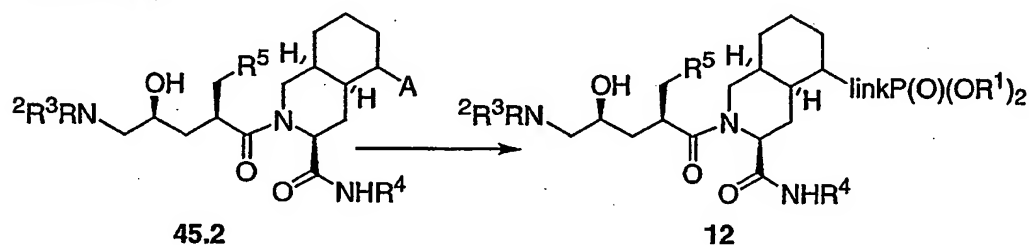
The reactions shown in Schemes 53 and 54 illustrate the preparation of the compounds 53.8 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],
30 [SH], [NH], Br. Scheme 55 depicts the conversion of the compounds 53.8 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 13 in which X and X' are sulfur. In this

procedure, the compounds 53.8 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 13.

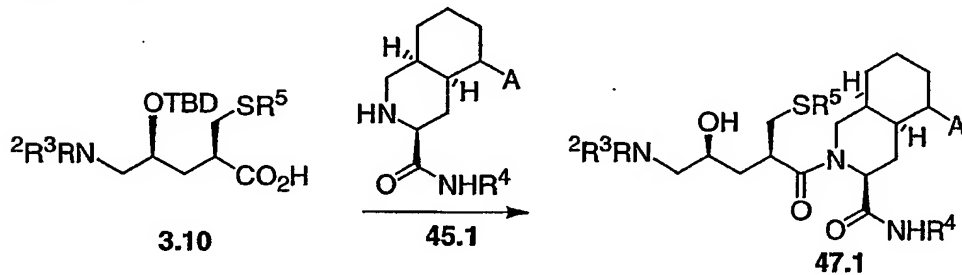
Scheme 45



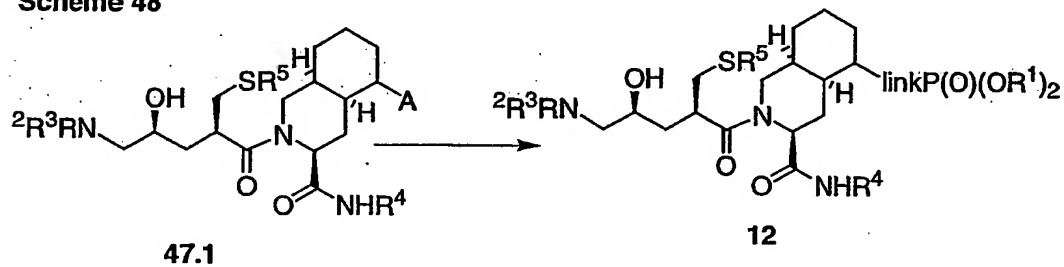
Scheme 46



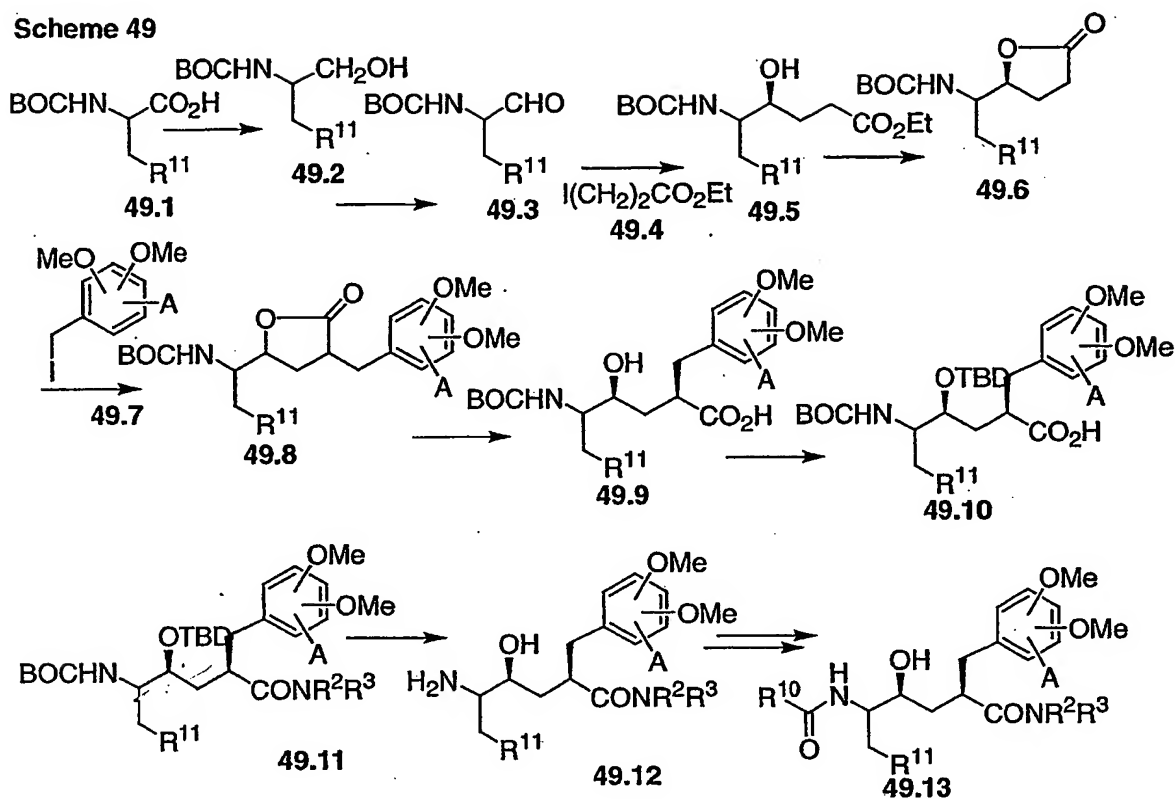
Scheme 47



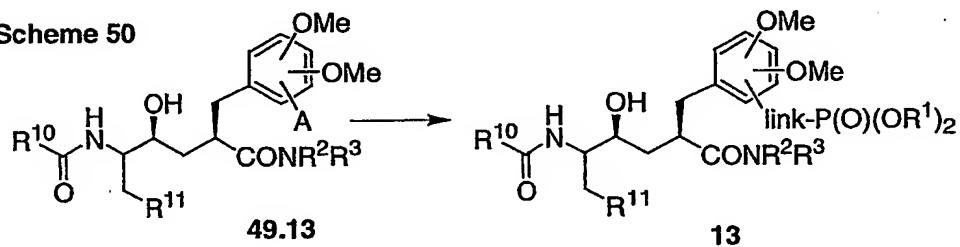
Scheme 48



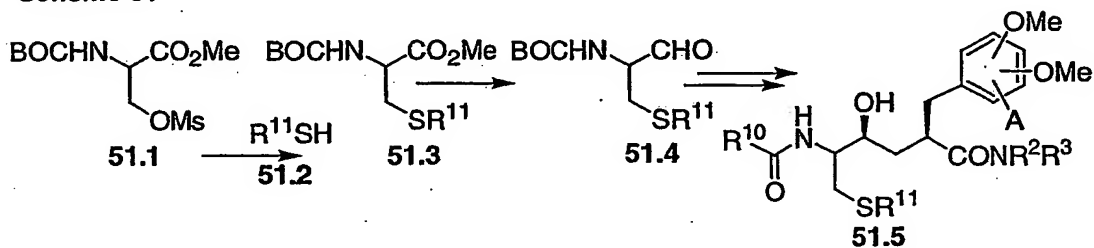
Scheme 49



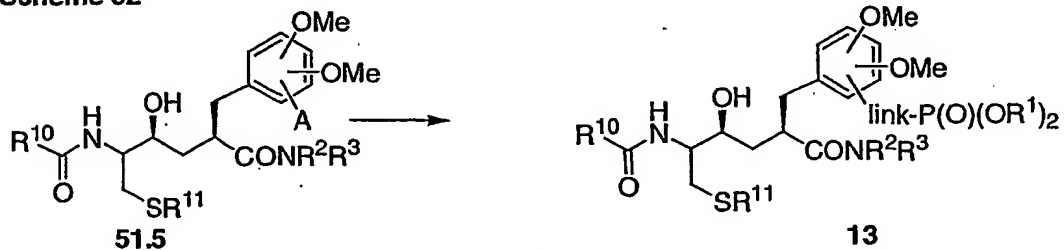
Scheme 50



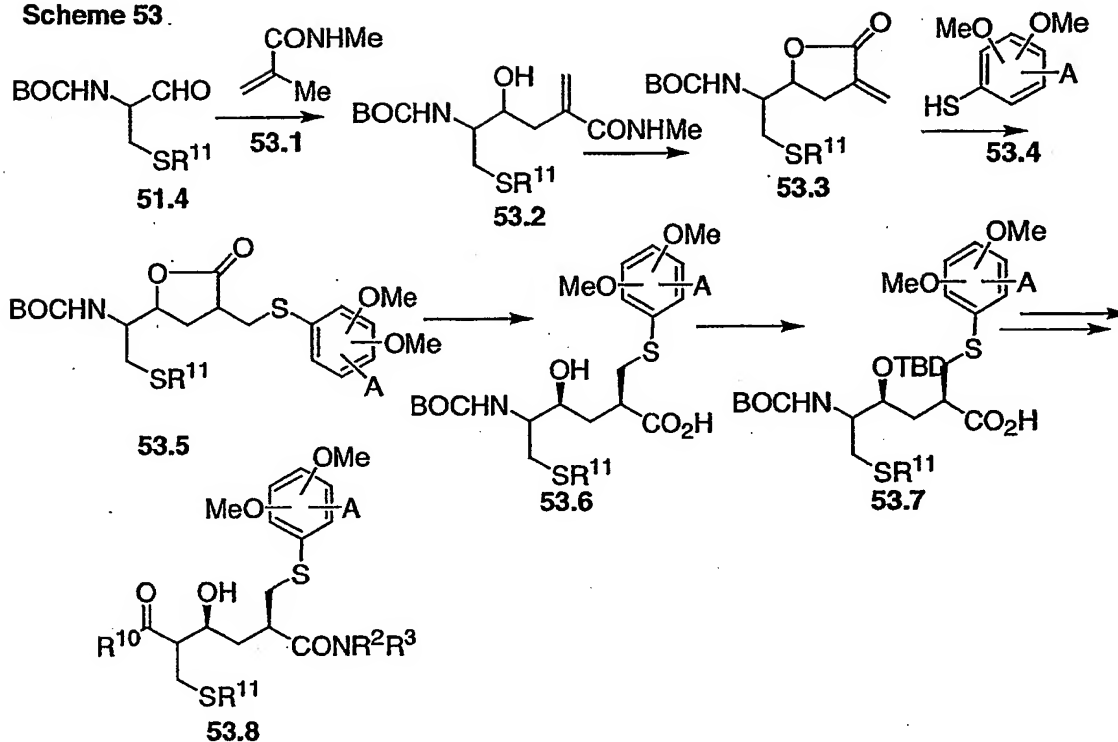
Scheme 51



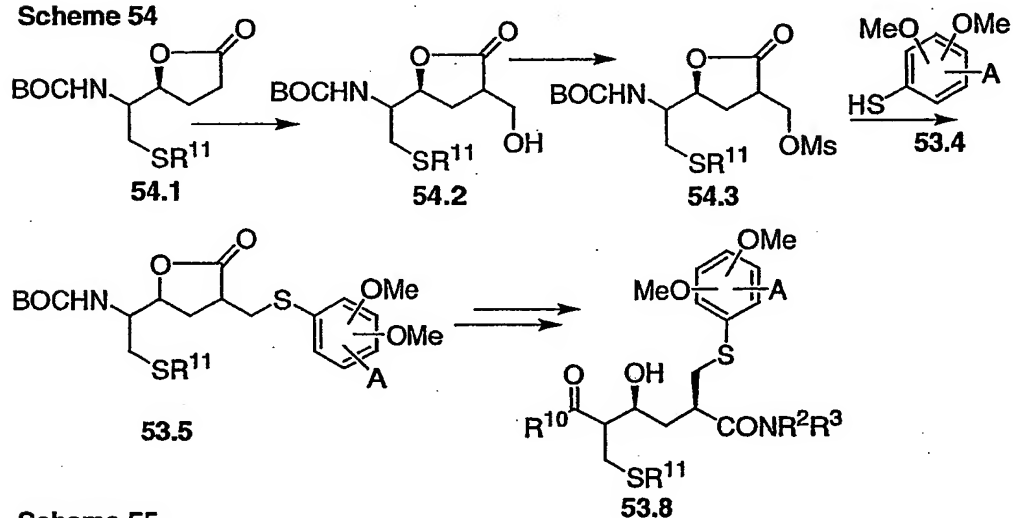
Scheme 52



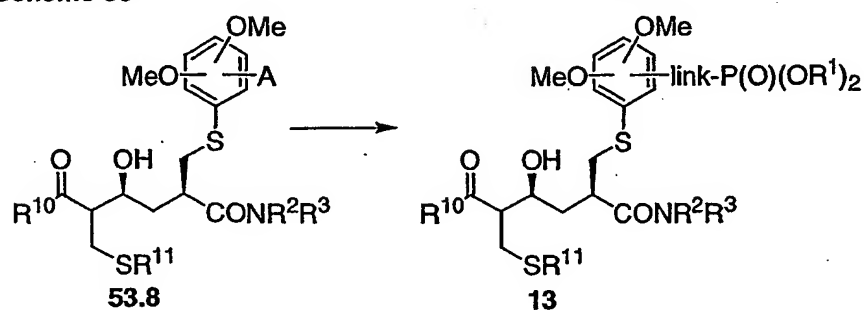
Scheme 53



Scheme 54



Scheme 55



Preparation of the phosphonate ester intermediates 13 in which X is sulfur and X' is a direct bond.

- 5 Schemes 56 and 57 illustrate the preparation of the phosphonate esters 13 in which X is sulfur and X' is a direct bond. In this procedure, the BOC-protected aldehyde 49.3 is converted, as described in Scheme 53, into the methylene lactone 56.1. The lactone is then reacted with the thiol 53.4 and a base, as described in Scheme 53, to yield the thioether 56.2. The thioether is then transformed, as described in Scheme 53, into the diamide 56.3.
- 10 The reactions shown in Scheme 56 illustrate the preparation of the compounds 56.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 57 depicts the conversion of the compounds 56.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 13 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 56.3 are converted, using the procedures described below,
- 15 Schemes 133 - 197, into the compounds 13.

Preparation of the phosphonate ester intermediates 14 in which X and X' are direct bonds.

- Schemes 58 and 59 illustrate the preparation of the phosphonate esters 14 in which X and X' are direct bonds. In this procedure, the lactone 49.6 is reacted, as described in Scheme 49,
- 20 with a substituted benzyl iodide 58.1, to produce the alkylated compound 58.2. The preparation of the benzyl iodides 58.1 is described in Schemes 187 - 191. The product is then transformed, as described in Scheme 49, into the diamide 58.3.
- The reactions shown in Scheme 58 illustrate the preparation of the compounds 58.3 in which
- 25 the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 59 depicts the conversion of the compounds 58.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 14 in which X and X' are direct bonds. In this procedure, the compounds 58.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 14.

30

Preparation of the phosphonate ester intermediates 14 in which X is a direct bond and X' is sulfur.

Schemes 60 and 61 illustrate the preparation of the phosphonate esters 14 in which X is a direct bond and X' is sulfur. In this procedure, the lactone 54.1 is reacted, as described in
5 Scheme 49, with a substituted benzyl iodide 58.1, to produce the alkylated compound 60.1. The product is then transformed, as described in Scheme 49, into the diamide 60.2.

The reactions shown in Scheme 60 illustrate the preparation of the compounds 60.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 61 depicts the conversion of the compounds 60.2 in which A is [OH],
10 [SH], [NH], Br, into the phosphonate esters 14 in which X is a direct bond and X' is sulfur. In this procedure, the compounds 60.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 14.

Preparation of the phosphonate ester intermediates 14 in which X and X' are sulfur.

15 Schemes 62, 63 and 64 illustrate the preparation of the phosphonate esters 14 in which X and X' are sulfur. As shown in Scheme 62, the methylene lactone 53.3 is reacted, as described in Scheme 53, with a substituted thiophenol 62.1 to produce the addition product 62.2. The preparation of the substituted thiophenols 62.1 is described below, (Schemes 144 - 153). The product is then transformed, as described in Scheme 53, into the diamide 62.3.

20 Scheme 63 illustrates an alternative method for the preparation of the diamide 62.3. In this procedure, the mesylate 54.3 is reacted, as described in Scheme 54, with the thiol 62.1 to afford the alkylation product 63.1. The product is then transformed, as described in Scheme 53, into the diamide 62.3.

The reactions shown in Schemes 62 and 63 illustrate the preparation of the compounds 62.3 in
25 which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 64 depicts the conversion of the compounds 62.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 14 in which X and X' are sulfur. In this procedure, the compounds 62.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 14.

Preparation of the phosphonate ester intermediates 14 in which X is sulfur and X' is a direct bond.

Schemes 65 and 66 illustrate the preparation of the phosphonate esters 14 in which X is sulfur and X' is a direct bond. In this procedure, the methylene lactone 56.1 is reacted, as described in Scheme 53, with a substituted thiophenol 62.1, to produce the thioether 65.1. The product is then transformed, as described in Scheme 53, into the diamide 65.2.

The reactions shown in Scheme 65 illustrate the preparation of the compounds 65.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 66 depicts the conversion of the compounds 65.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 14 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 65.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 14.

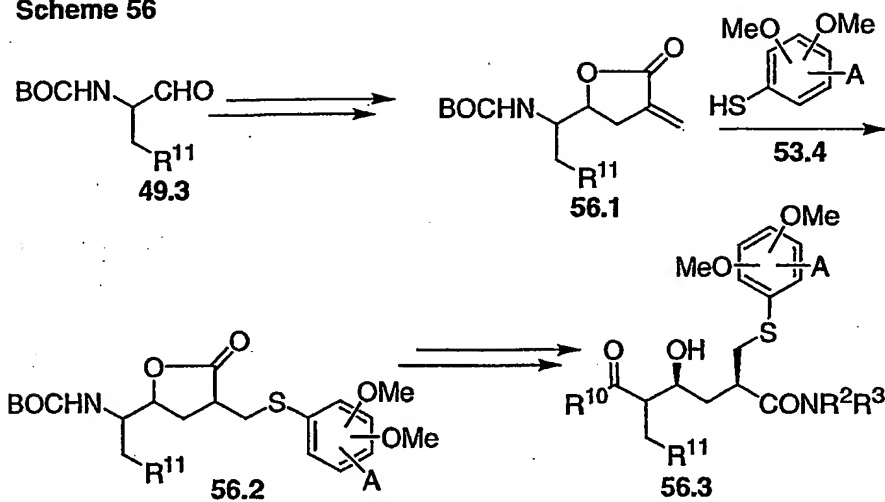
Preparation of the phosphonate ester intermediates 15 in which X and X' are direct bonds.

Schemes 67 and 68 illustrate the preparation of the phosphonate esters 15 in which X and X' are direct bonds. In this procedure, the BOC-protected phenylalanine derivative 67.1 is converted into the corresponding aldehyde 67.2, using the procedures described above (Scheme 49). The preparation of the phenylalanine derivatives 67.1 is described below, (Schemes 182 - 184). The aldehyde is then converted, using the procedures described in Scheme 49, into the lactone 67.3. The latter compound is then alkylated, as described in Scheme 49, with the reagent R⁵CH₂I, (67.4), to afford the alkylated product 67.5. This compound is then converted, as described in Scheme 49, into the diamide 67.6.

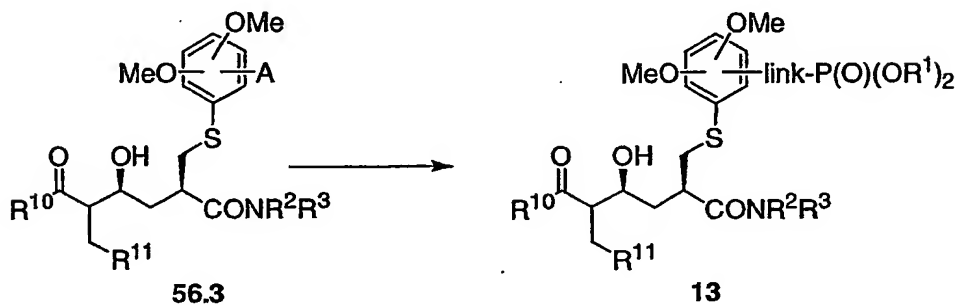
The reactions shown in Scheme 67 illustrate the preparation of the compounds 67.6 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 68 depicts the conversion of the compounds 67.6 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 15 in which X and X' are direct bonds. In this

procedure, the compounds **67.6** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **15**.

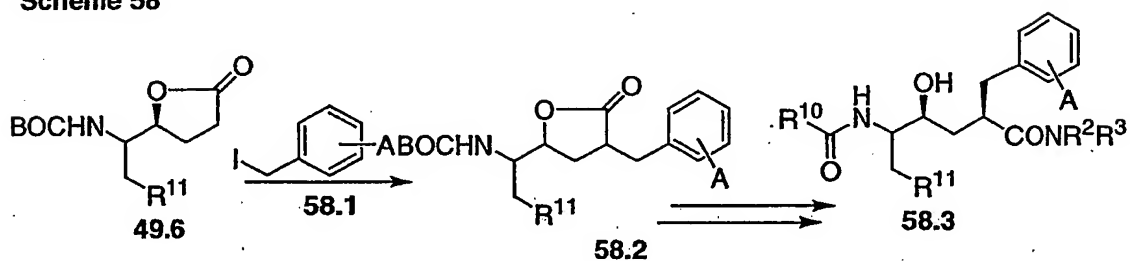
Scheme 56



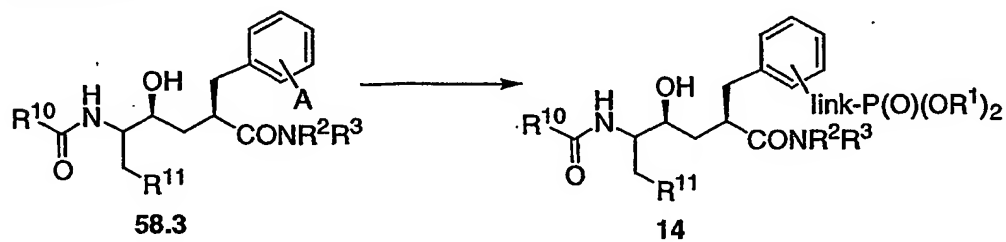
Scheme 57



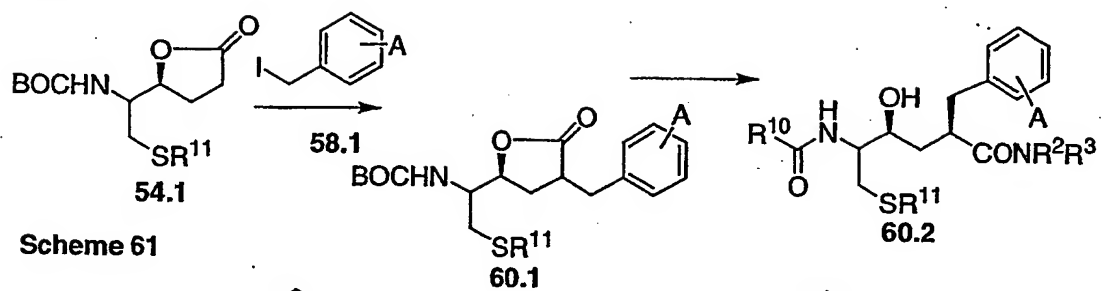
Scheme 58



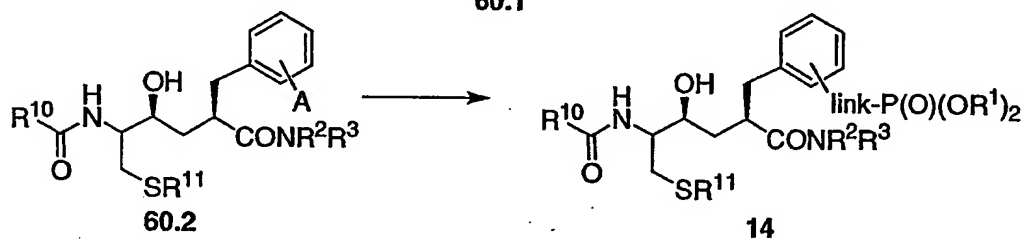
Scheme 59



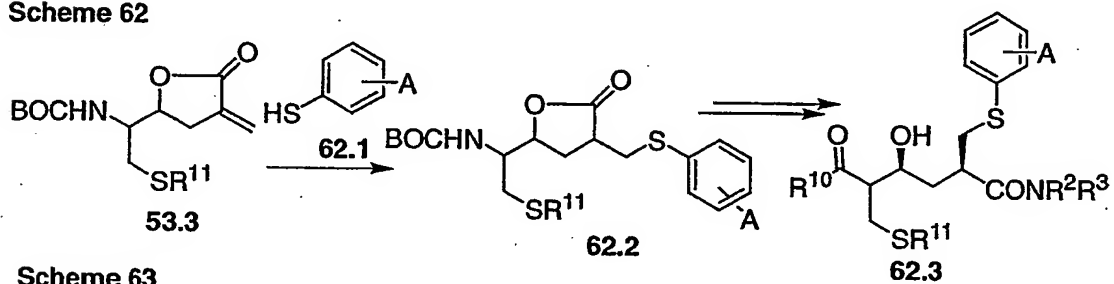
Scheme 60



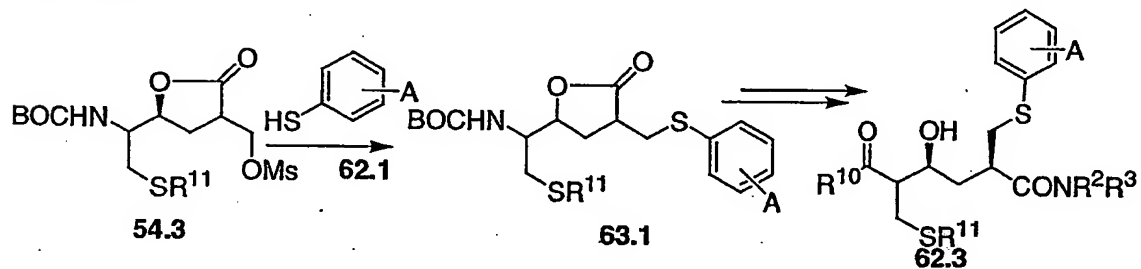
Scheme 61



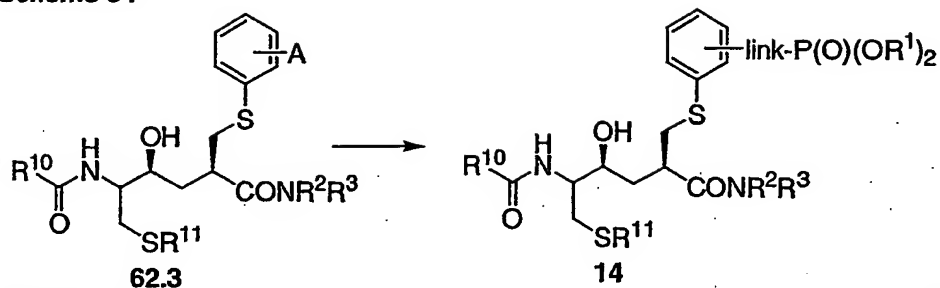
Scheme 62



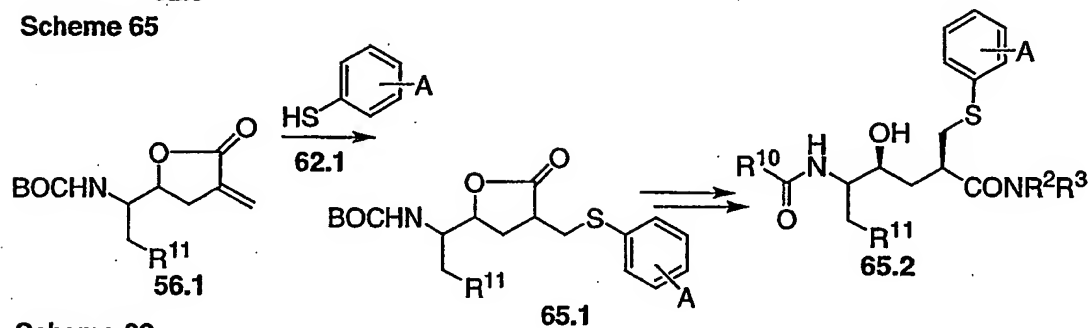
Scheme 63



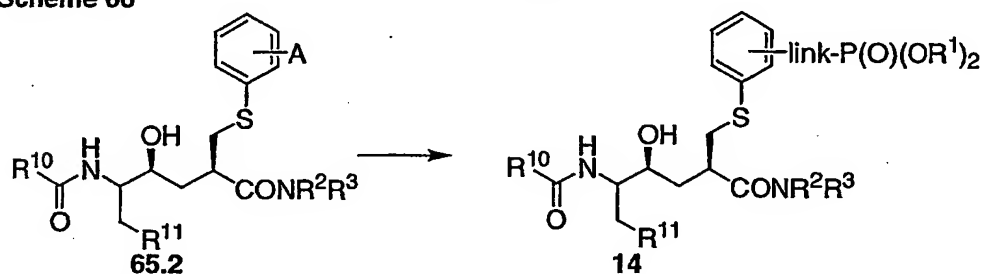
Scheme 64



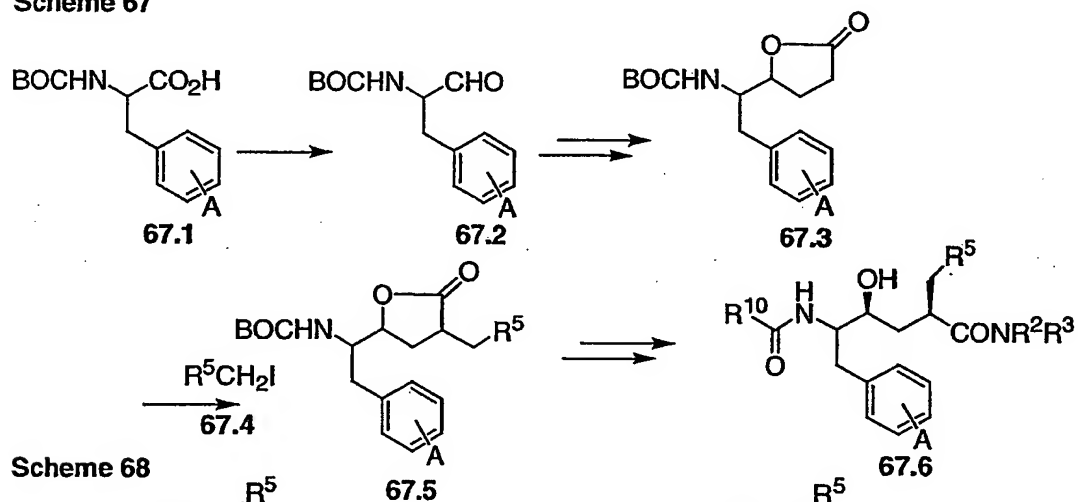
Scheme 65



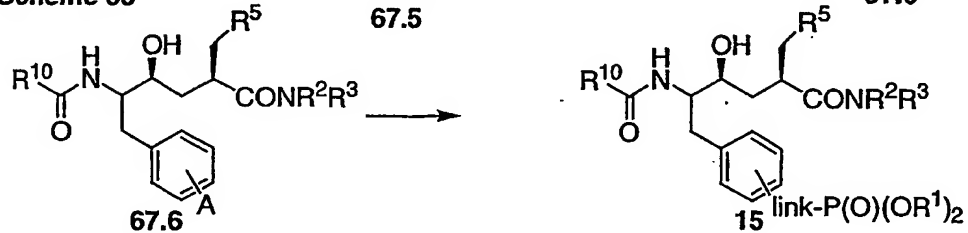
Scheme 66



Scheme 67



Scheme 68



Preparation of the phosphonate ester intermediates 15 in which X is a direct bond and X' is sulfur.

Schemes 69 and 70 illustrate the preparation of the phosphonate esters 15 in which X is a direct bond and X' is sulfur. In this procedure, the mesylate 51.1 is reacted, as described in
5 Scheme 51, with the thiophenol derivative 69.1. The preparation of the thiophenol derivatives 69.1 is described below, Schemes 144 – 153. The product is then converted, as described in Scheme 51, into the corresponding aldehyde 69.3, and the latter compound is then transformed, as described in Scheme 49, into the lactone 69.4. The lactone is then alkylated, as described in Scheme 49, with the reagent R^5CH_2I , (67.4), to afford the alkylated product
10 69.5. This compound is then converted, as described in Scheme 49, into the diamide 69.6.

The reactions shown in Scheme 69 illustrate the preparation of the compounds 69.6 in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 70 depicts the conversion of the compounds 69.6 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 15 in which X is a direct bond and X' is sulfur. In this
15 procedure, the compounds 69.6 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 15.

Preparation of the phosphonate ester intermediates 15 in which X and X' are sulfur.

Schemes 71, 72 and 73 illustrate the preparation of the phosphonate esters 15 in which X and
20 X' are sulfur. As shown in Scheme 71, the aldehyde 69.3 is converted, as described in Scheme 53, into the methylene lactone 71.1. The lactone is then reacted, as described in Scheme 53, with the thiol reagent 71.2 to yield the thioether product 71.3. The product is then transformed, as described in Scheme 53, into the diamide 71.4.

Scheme 72 illustrates an alternative method for the preparation of the diamide 71.4. In this
25 procedure, the lactone 69.4 is reacted, as described in Scheme 54, with formaldehyde or a formaldehyde equivalent, to afford the hydroxymethyl product 72.1. The product is then transformed, by mesylation followed by reaction of the mesylate with the thiol reagent 71.2, using the procedures described in Scheme 53, into the thioether 71.3. The latter compound is then converted, as described in Scheme 53, into the diamide 71.4.

The reactions shown in Schemes 71 and 72 illustrate the preparation of the compounds 71.4 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 73 depicts the conversion of the compounds 71.4 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 15 in which X and X' are sulfur. In this procedure, the compounds 71.4 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 15.

Preparation of the phosphonate ester intermediates 15 in which X is sulfur and X' is a direct bond.

- 10 Schemes 74 and 75 illustrate the preparation of the phosphonate esters 15 in which X is sulfur and X' is a direct bond. In this procedure, the aldehyde 67.2 is converted, as described in Scheme 53, into the methylene lactone 74.1. The lactone is then reacted, as described in Scheme 53, with the thiol 71.2 to afford the thioether 74.2. This compound is then converted, as described in Scheme 53, into the diamide 74.3.
- 15 The reactions shown in Schemes 74 illustrate the preparation of the compounds 74.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 75 depicts the conversion of the compounds 74.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 15 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 74.3 are converted, using the procedures described below,
- 20 Schemes 133 - 197, into the compounds 15.

Preparation of the phosphonate ester intermediates 16 in which X and X' are direct bonds.

- 25 Schemes 76 and 77 illustrate the preparation of the phosphonate esters 16 in which X and X' are direct bonds. In this procedure, the lactone 49.6 is reacted, as described in Scheme 49, with the iodo compound 67.4 to yield the alkylated lactone 76.1. The lactone is then converted, as described in Scheme 49, into the carboxylic acid 76.2. The carboxylic acid is then coupled, as described in Scheme 1, with the aminoindanol derivative 1.2 to afford the amide 76.3. The latter compound is then converted, as described in Scheme 49, into the
- 30 diamide 76.4.

The reactions shown in Scheme 76 illustrate the preparation of the compounds 76.4 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 77 depicts the conversion of the compounds 76.4 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 16 in which X and X' are direct bonds. In this
5 procedure, the compounds 76.4 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 16.

Preparation of the phosphonate ester intermediates 16 in which X is a direct bond and X' is sulfur.

- 10 Schemes 78 and 79 illustrate the preparation of the phosphonate esters 16 in which X is a direct bond and X' is sulfur. In this procedure, the lactone 54.1 is reacted, as described in Scheme 49, with the iodo compound 67.4, to produce the alkylated compound 78.1. This material is then transformed, as described in Scheme 49, into the carboxylic acid 78.2, which is then transformed, as described in Scheme 76, into the diamide 78.3.
- 15 The reactions shown in Scheme 78 illustrate the preparation of the compounds 78.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 79 depicts the conversion of the compounds 78.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 16 in which X is a direct bond and X' is sulfur. In this procedure, the compounds 78.3 are converted, using the procedures described below,
20 Schemes 133 - 197, into the compounds 16.

Preparation of the phosphonate ester intermediates 16 in which X and X' are sulfur.

- Schemes 80, 81 and 82 illustrate the preparation of the phosphonate esters 15 in which X and X' are sulfur. As shown in Scheme 80, the methylene lactone 53.3 is reacted with the thiol
25 71.2 to produce the thioether 80.1. The compound is then transformed, as described in Scheme 49, into the silyl-protected carboxylic acid 80.2. This material is then converted, as described in Scheme 76, into the diamide 80.3.

Scheme 81 illustrates an alternative method for the preparation of the compounds 80.2. In this procedure, the mesylate 54.3 is reacted, as described in Scheme 54, with the thiol 71.2, to

prepare the thioether **80.1**. The product is then transformed, as described in Scheme 54, into the diamide **80.3**.

The reactions shown in Schemes **80** and **81** illustrate the preparation of the compounds **80.3** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],

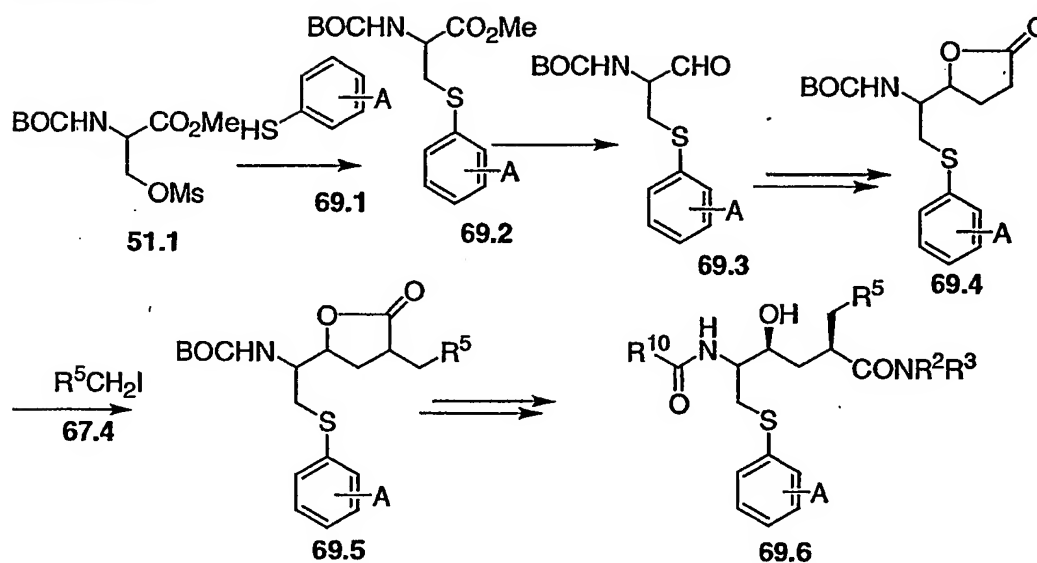
- 5 [SH], [NH], Br. Scheme **82** depicts the conversion of the compounds **80.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **16** in which X and X' are sulfur. In this procedure, the compounds **80.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **16**.

- 10 **Preparation of the phosphonate ester intermediates 16 in which X is sulfur and X' is a direct bond.**

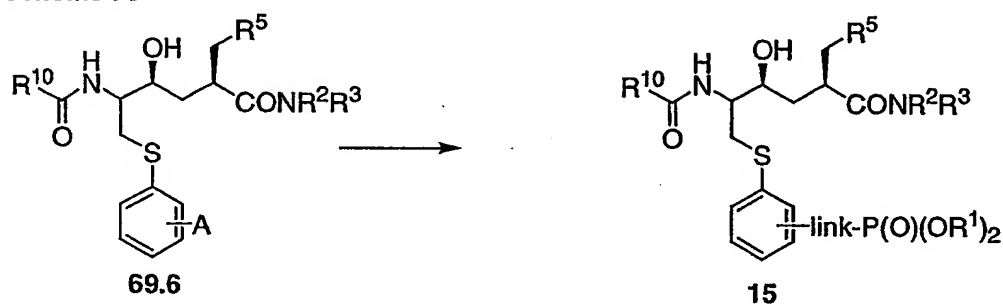
- Schemes **83** and **84** illustrate the preparation of the phosphonate esters **16** in which X is sulfur and X' is a direct bond. In this procedure, the methylene lactone **53.3** is reacted, as described in Scheme **53**, with the thiol **71.2** to yield the thioether **83.1**. The product is then converted,
15 as described in Scheme **76**, into the diamide **83.2**.

- The reactions shown in Scheme **83** illustrate the preparation of the compounds **83.2** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme **84** depicts the conversion of the compounds **83.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **16** in which X is sulfur and X' is a direct bond. In this
20 procedure, the compounds **83.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **16**.

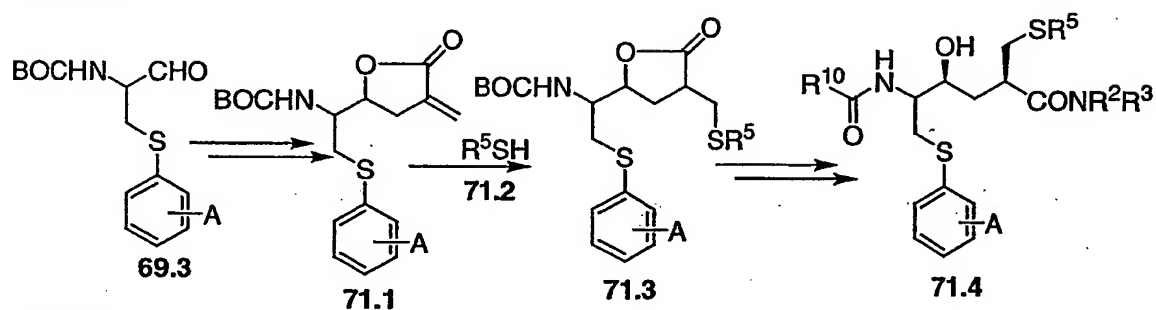
Scheme 69



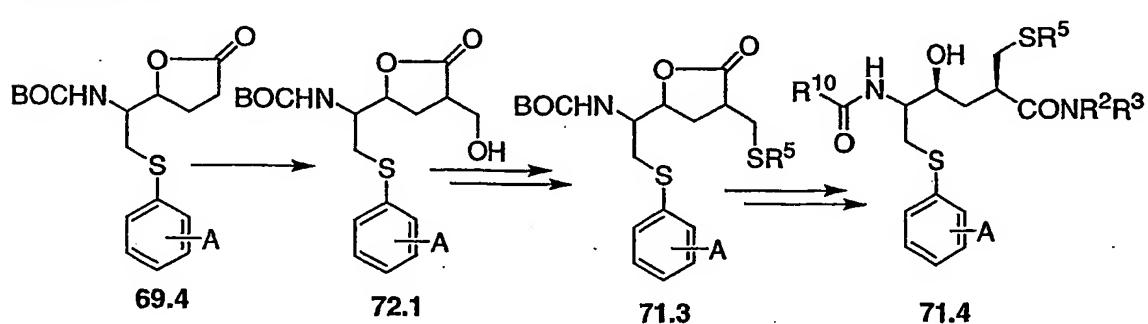
Scheme 70



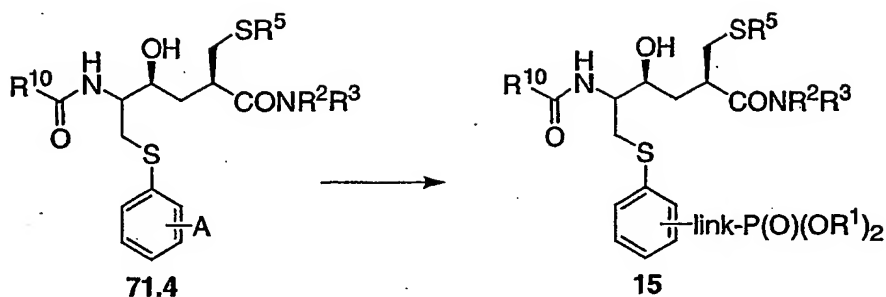
Scheme 71



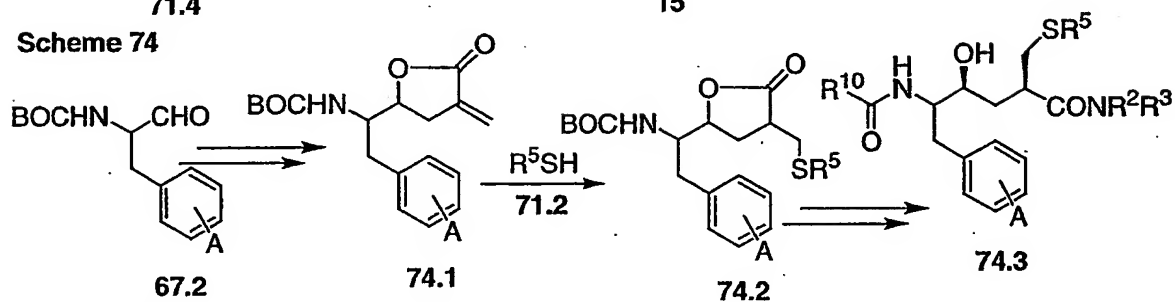
Scheme 72



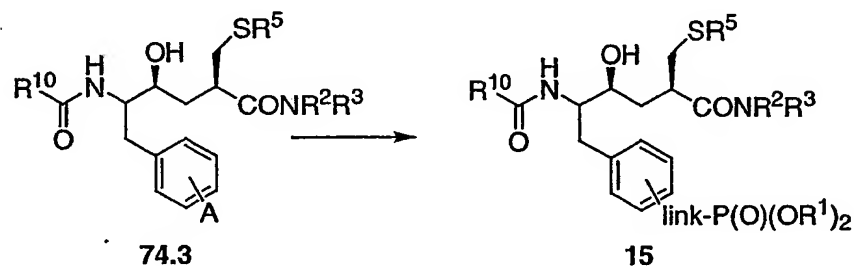
Scheme 73



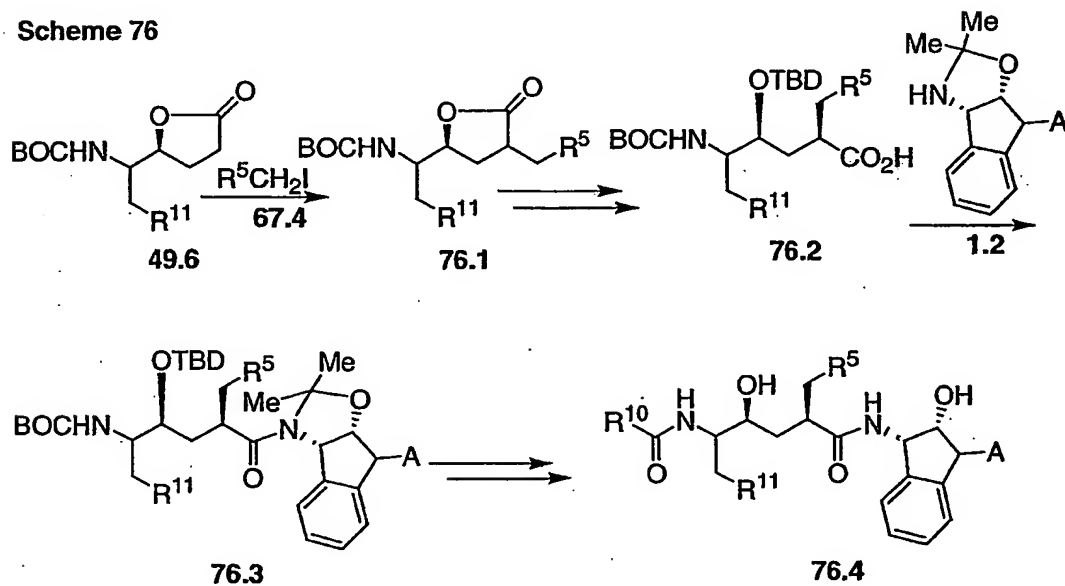
Scheme 74



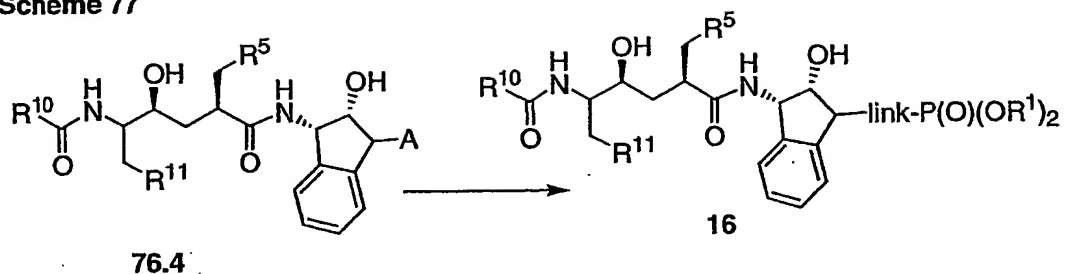
Scheme 75



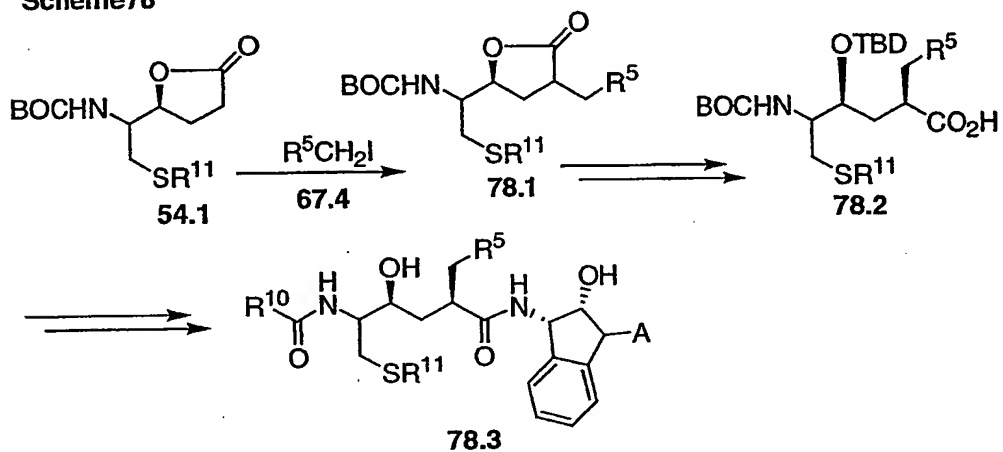
Scheme 76



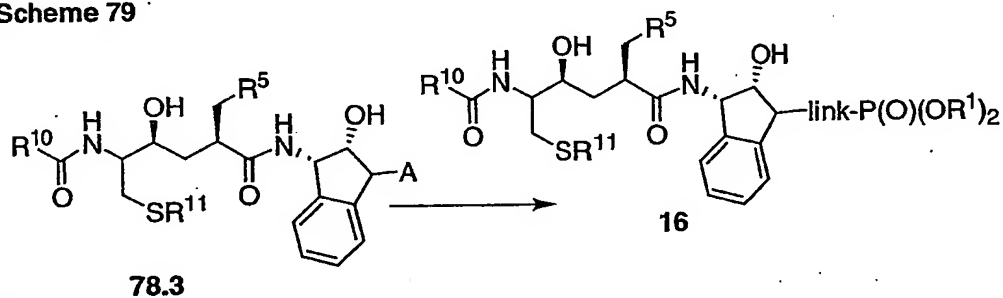
Scheme 77



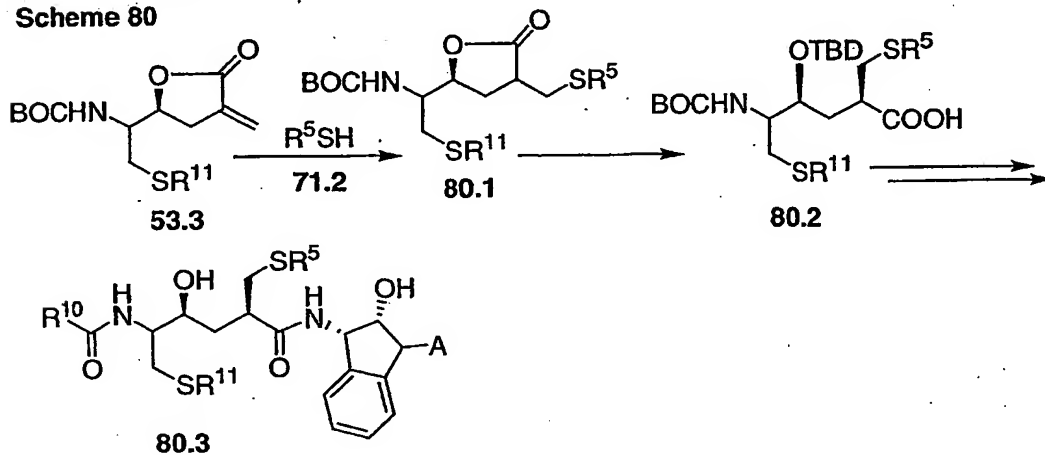
Scheme 78



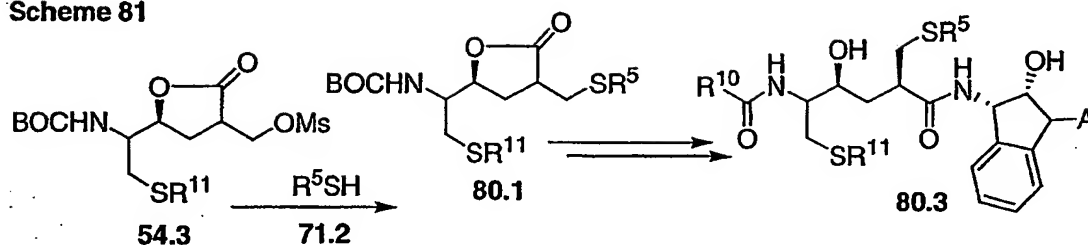
Scheme 79



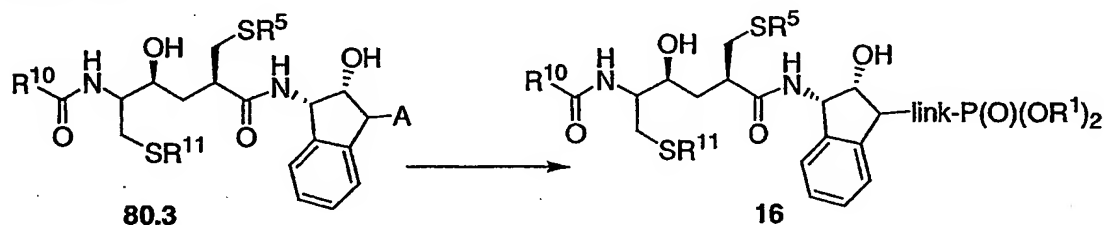
Scheme 80



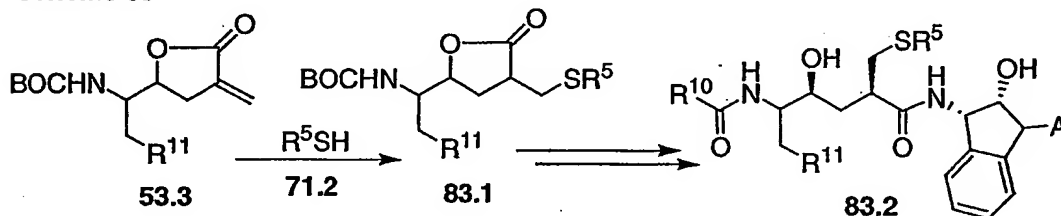
Scheme 81



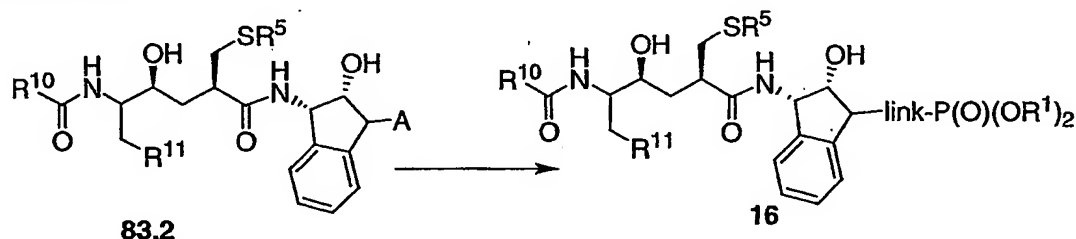
Scheme 82



Scheme 83



Scheme 84



Preparation of the phosphonate ester intermediates 17 in which X and X' are direct bonds.

Schemes 85 and 86 illustrate the preparation of the phosphonate esters 17 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in Scheme 1, with the aminochroman derivative 33.1 to afford the amide 85.1. The product is then converted, as described in Scheme 49, into the diamide 85.2.

The reactions shown in Scheme 85 illustrate the preparation of the compounds 85.2 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 86 depicts the conversion of the compounds 85.2 in which A is [OH], [SH],

[NH], Br, into the phosphonate esters 17 in which X and X' are direct bonds. In this procedure, the compounds 85.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 17.

5 Preparation of the phosphonate ester intermediates 17 in which X is a direct bond and X' is sulfur.

Schemes 87 and 88 illustrate the preparation of the phosphonate esters 17 in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid 78.2 is coupled with the amine 33.1 to afford the amide 87.1. The product is then converted, as described in Scheme 49, into the diamide 87.2.

The reactions shown in Scheme 87 illustrate the preparation of the compounds 87.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 88 depicts the conversion of the compounds 87.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 17 in which X is a direct bond and X' is sulfur. In this procedure, the compounds 87.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 17.

Preparation of the phosphonate ester intermediates 17 in which X and X' are sulfur.

Schemes 89 and 90 illustrate the preparation of the phosphonate esters 17 in which X and X' are sulfur. As shown in Scheme 89, the carboxylic acid 80.2 is coupled, as described in Scheme 1, with the chroman amine 33.1 to give the amide 89.1. The product is then transformed, as described in Scheme 49, into the diamide 89.2.

The reactions shown in Scheme 89 illustrate the preparation of the compounds 89.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 90 depicts the conversion of the compounds 89.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 17 in which X and X' are sulfur. In this procedure, the compounds 89.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 17.

Preparation of the phosphonate ester intermediates 17 in which X is sulfur and X' is a direct bond.

Schemes 91 and 92 illustrate the preparation of the phosphonate esters 17 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1, which is an intermediate compound in the conversion of the lactone 83.1 into the diamide 83.2, (Scheme 83), is
5 coupled, as described in Scheme 1, with the chroman amine 33.1 to afford the amide 91.2. The product is then converted, as described in Scheme 49, into the diamide 91.3.

The reactions shown in Scheme 91 illustrate the preparation of the compounds 91.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH],
10 [NH], Br. Scheme 92 depicts the conversion of the compounds 91.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 17 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 91.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 17.

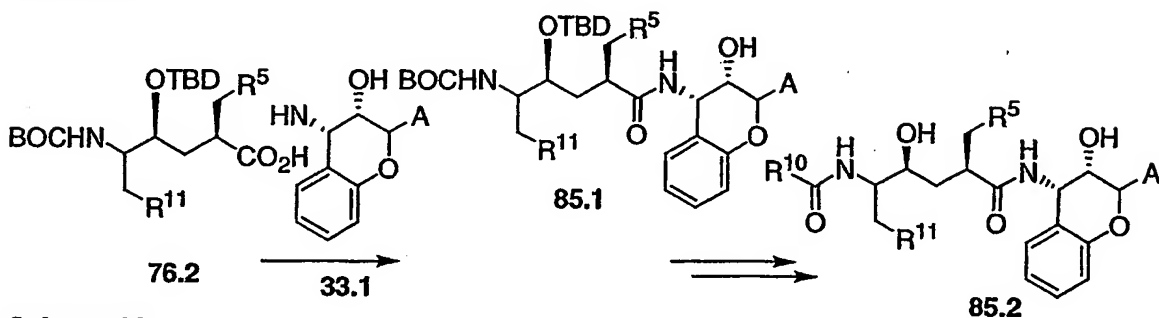
15 Preparation of the phosphonate ester intermediates 18 in which X and X' are direct bonds.

Schemes 93 and 94 illustrate the preparation of the phosphonate esters 18 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in Scheme 1, with the ethanolamine derivative 29.1 to afford the amide 93.1. The product is then converted, as described in Scheme 49, into the diamide 93.2.

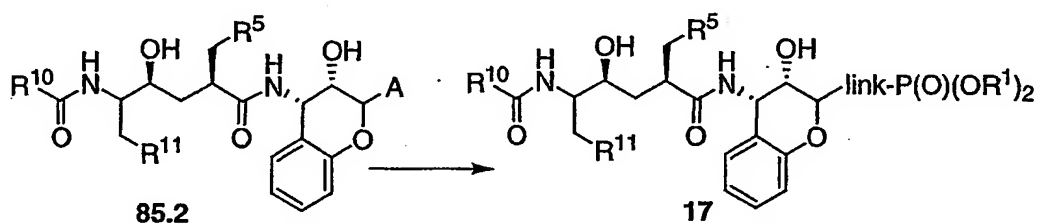
20 The reactions shown in Scheme 93 illustrate the preparation of the compounds 93.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 94 depicts the conversion of the compounds 93.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 18 in which X and X' are direct bonds. In this procedure, the compounds 93.2 are converted, using the procedures described below,
25 Schemes 133 - 197, into the compounds 18.

Preparation of the phosphonate ester intermediates 18 in which X and X' are sulfur.

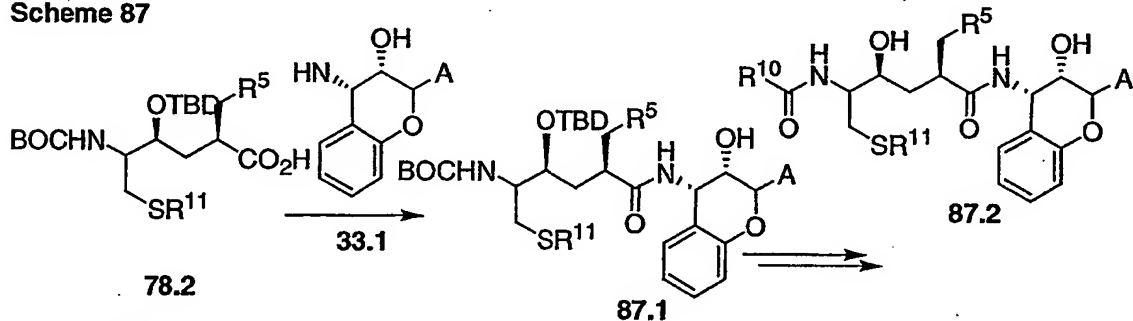
Scheme 85



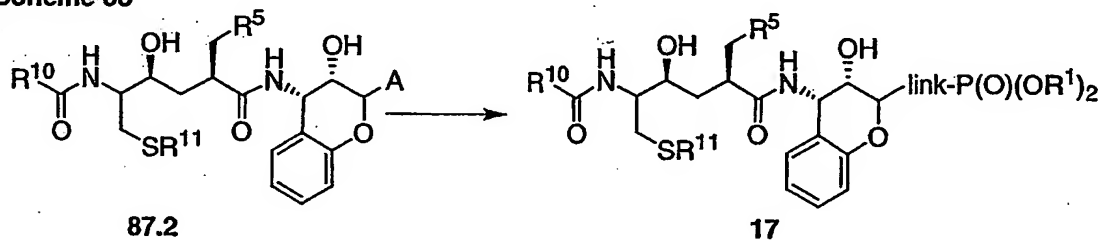
Scheme 86



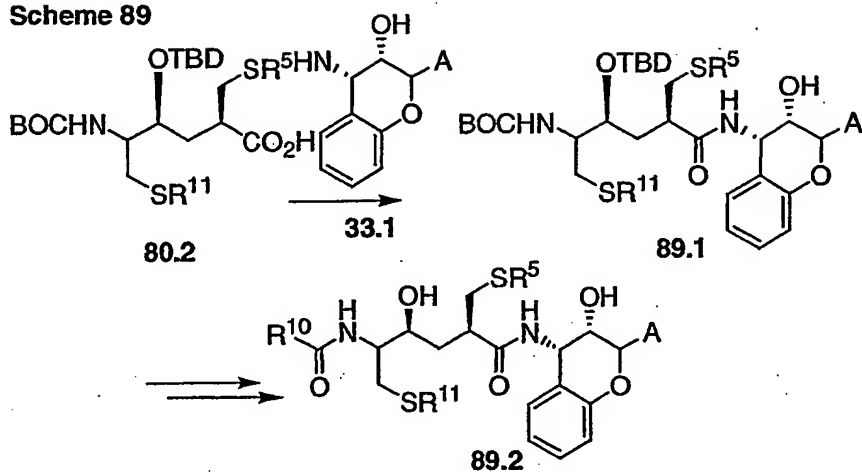
Scheme 87



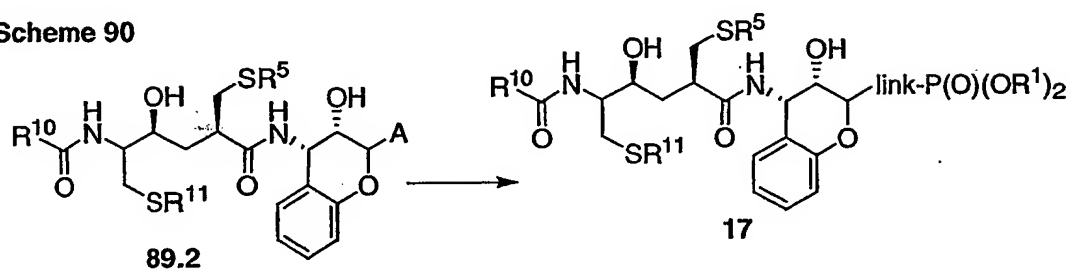
Scheme 88



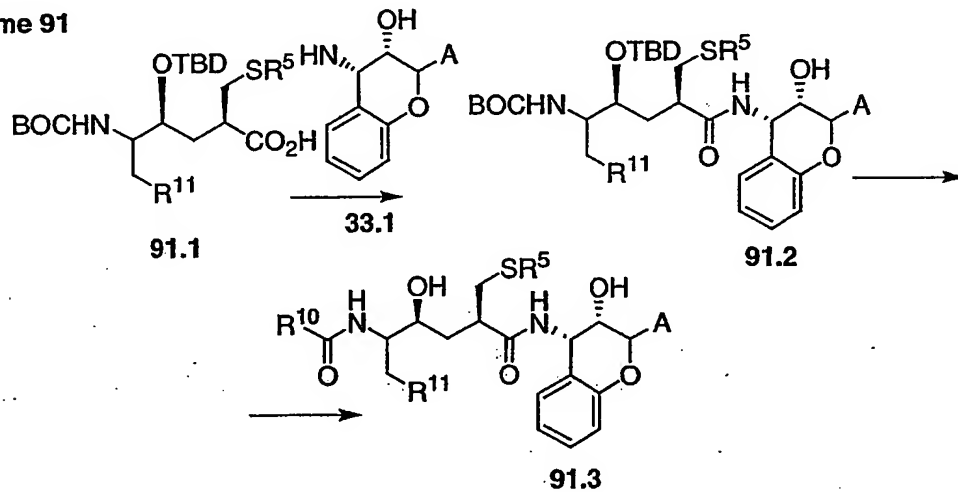
Scheme 89



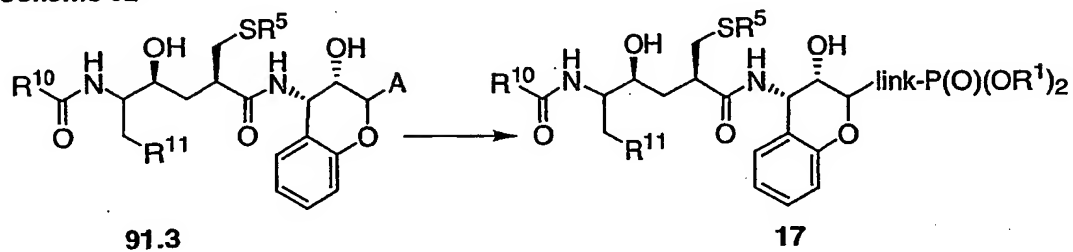
Scheme 90



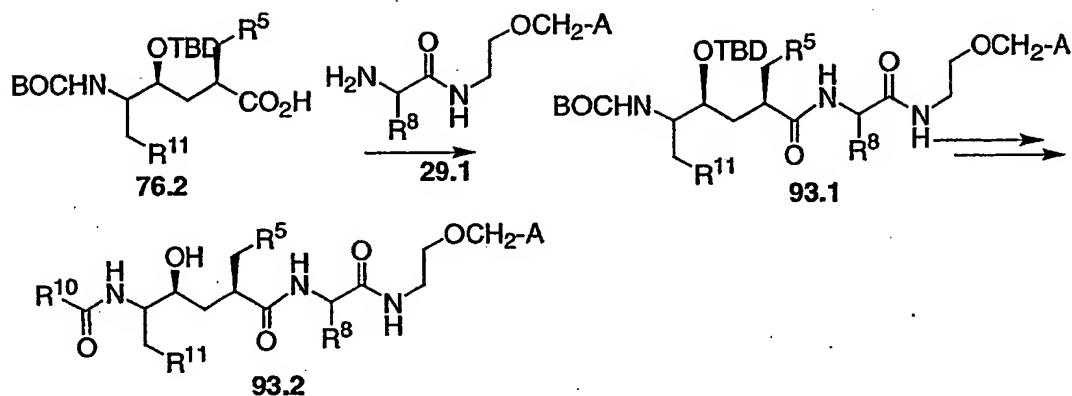
Scheme 91



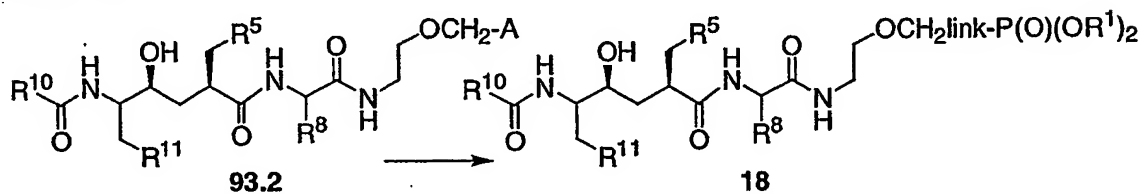
Scheme 92



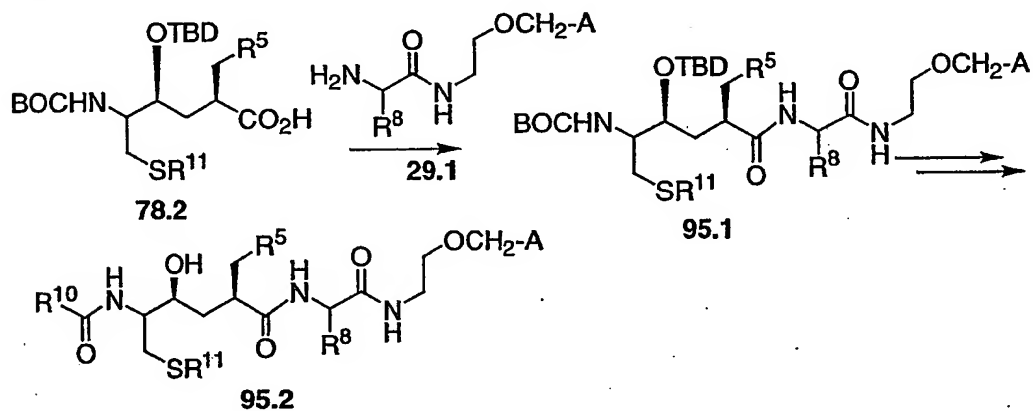
Scheme 93



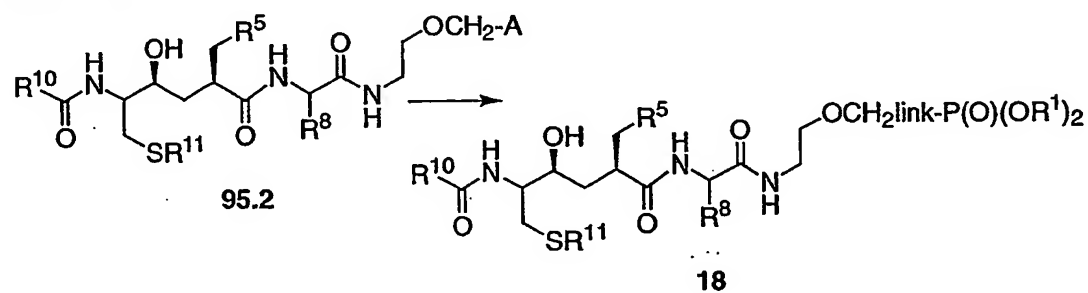
Scheme 94



Scheme 95



Scheme 96



Schemes 97 and 98 illustrate the preparation of the phosphonate esters 18 in which X and X' are sulfur. As shown in Scheme 97, the carboxylic acid 80.2 is coupled, as described in Scheme 1, with the ethanolamine derivative 29.1 to give the amide 97.1. The product is then transformed, as described in Scheme 49, into the diamide 97.2.

- 5 The reactions shown in Scheme 97 illustrate the preparation of the compounds 97.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 98 depicts the conversion of the compounds 97.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 18 in which X and X' are sulfur. In this procedure, the compounds 97.2 are converted, using the procedures described below, Schemes 133 - 197,
10 into the compounds 18.

Preparation of the phosphonate ester intermediates 18 in which X is sulfur and X' is a direct bond.

- Schemes 99 and 100 illustrate the preparation of the phosphonate esters 18 in which X is
15 sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the ethanolamine derivative 29.1 to afford the amide 99.1. The product is then converted, as described in Scheme 49, into the diamide 99.2.

- The reactions shown in Scheme 99 illustrate the preparation of the compounds 99.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH],
20 [NH], Br. Scheme 100 depicts the conversion of the compounds 99.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 18 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 99.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 18.

- 25 **Preparation of the phosphonate ester intermediates 19 in which X and X' are direct bonds.**

Schemes 101 and 102 illustrate the preparation of the phosphonate esters 19 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in

Scheme 1, with the phenylalanine derivative 37.1 to afford the amide 101.1. The product is then converted, as described in Scheme 49, into the diamide 101.2.

The reactions shown in Scheme 101 illustrate the preparation of the compounds 101.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 102 depicts the conversion of the compounds 101.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 19 in which X and X' are direct bonds. In this procedure, the compounds 101.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 19.

10 Preparation of the phosphonate ester intermediates 19 in which X is a direct bond and X' is sulfur.

Schemes 103 and 104 illustrate the preparation of the phosphonate esters 19 in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid 78.2 is coupled, as described in Scheme 1, with the amine 37.1 to afford the amide 103.1. The product is then converted, as described in Scheme 49, into the diamide 103.2.

The reactions shown in Scheme 103 illustrate the preparation of the compounds 103.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 104 depicts the conversion of the compounds 103.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 19 in which X is a direct bond and X' is sulfur. In this procedure, the compounds 103.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 19.

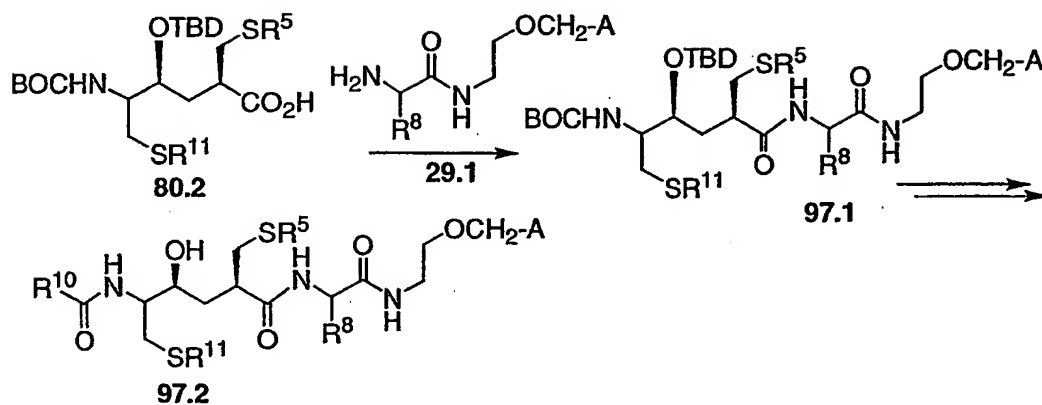
Preparation of the phosphonate ester intermediates 19 in which X and X' are sulfur.

Schemes 105 and 106 illustrate the preparation of the phosphonate esters 19 in which X and X' are sulfur. As shown in Scheme 105, the carboxylic acid 80.2 is coupled, as described in Scheme 1, with the phenylalanine derivative 37.1 to give the amide 105.1. The product is then transformed, as described in Scheme 49, into the diamide 105.2.

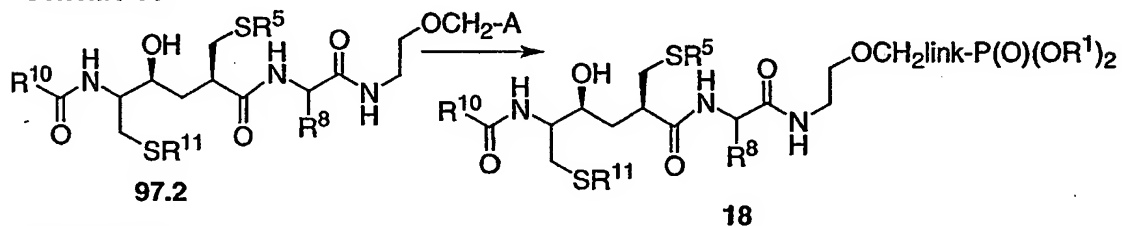
The reactions shown in Scheme 105 illustrate the preparation of the compounds 105.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],

[SH], [NH], Br. Scheme **106** depicts the conversion of the compounds **105.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **19** in which X and X' are sulfur. In this procedure, the compounds **105.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **19**.

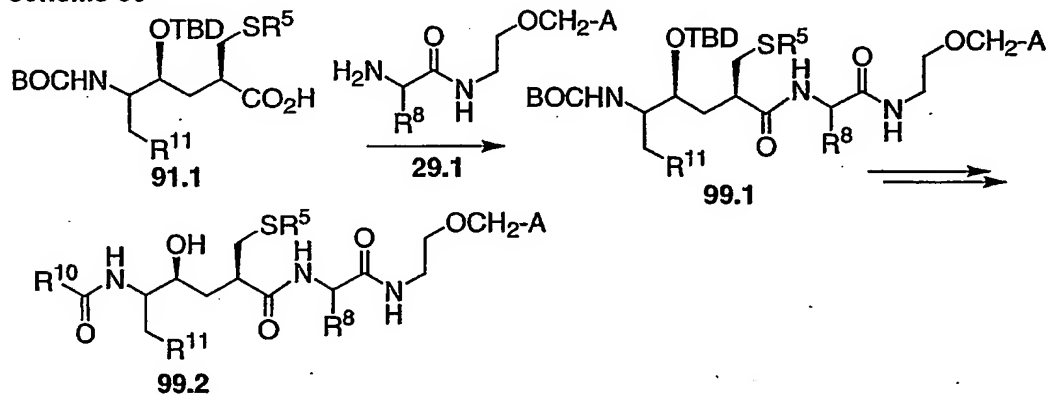
Scheme 97



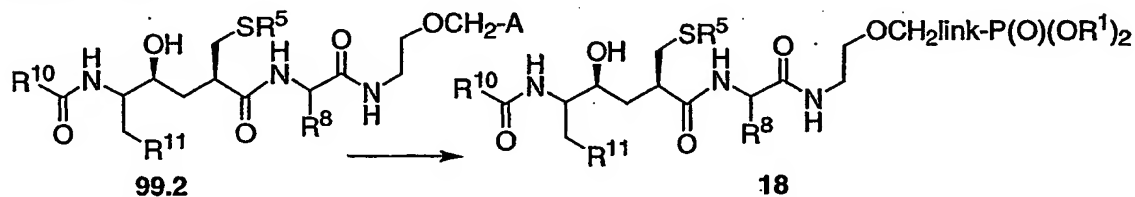
Scheme 98



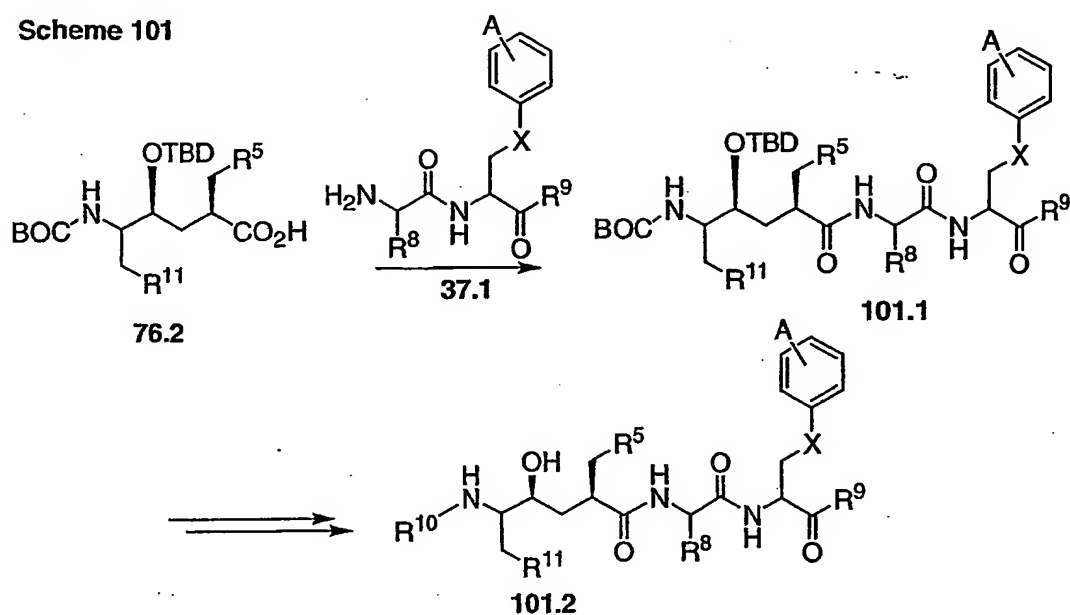
Scheme 99



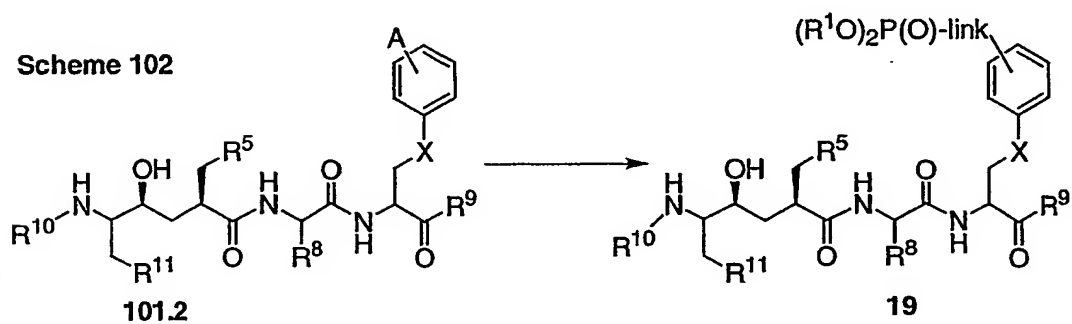
Scheme 100



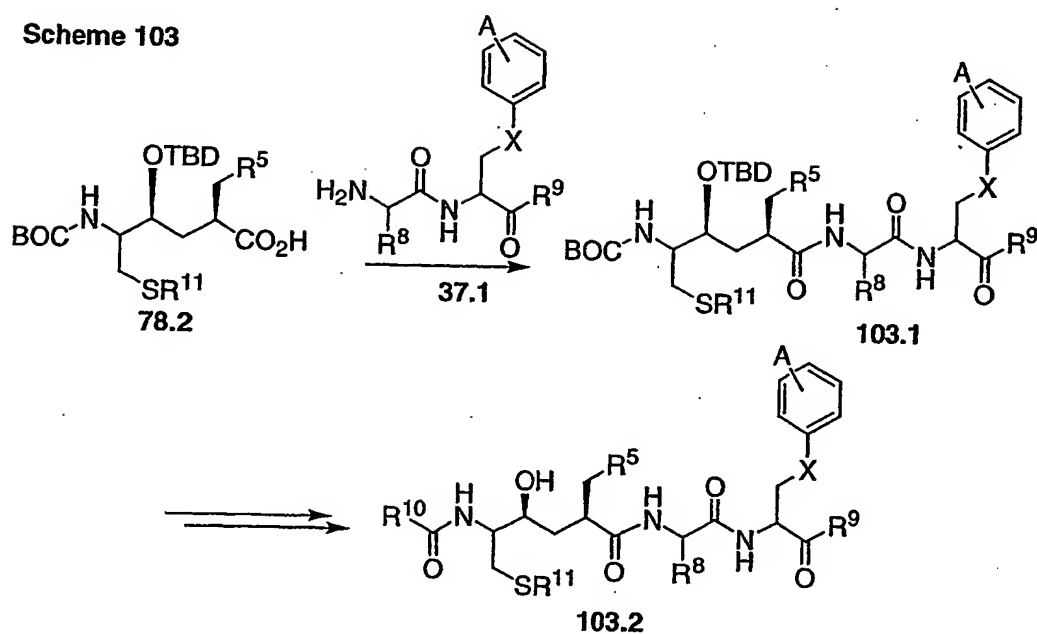
Scheme 101



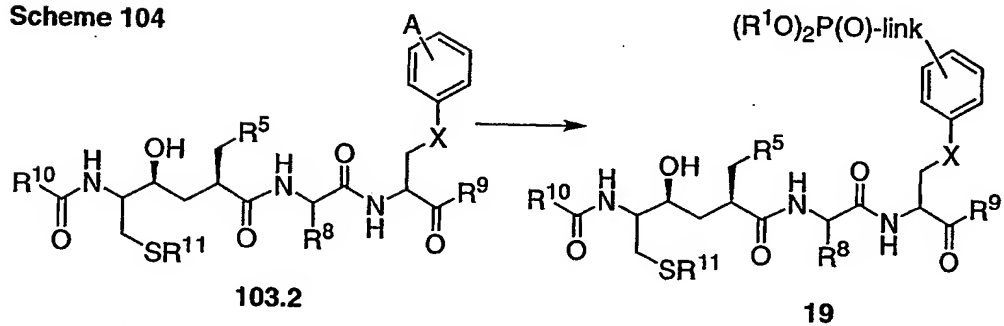
Scheme 102



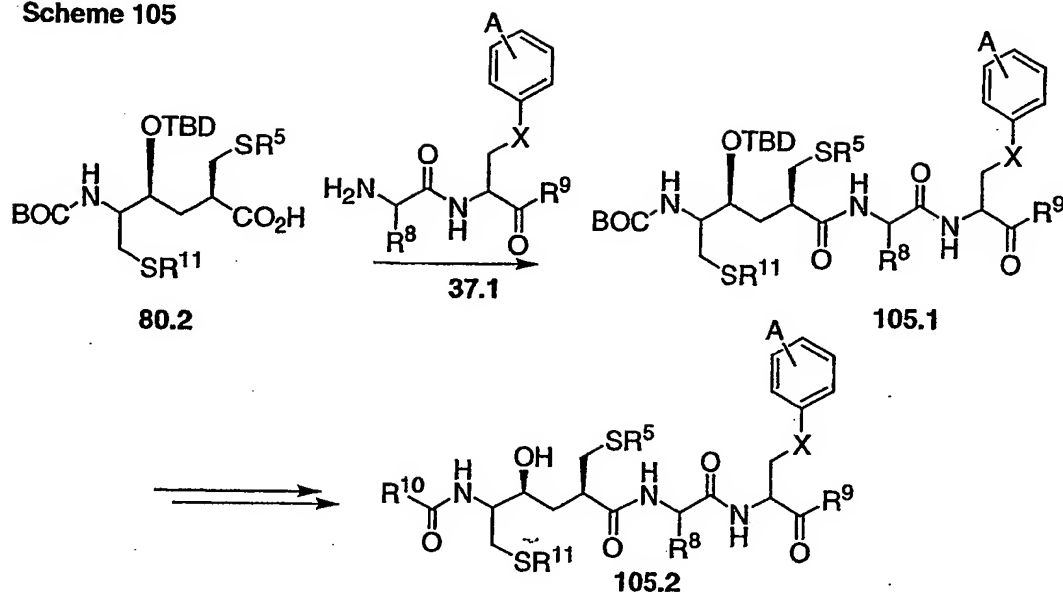
Scheme 103



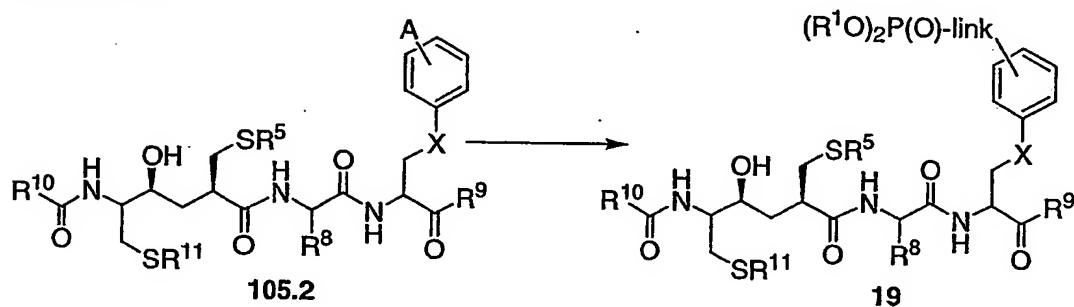
Scheme 104



Scheme 105



Scheme 106



Preparation of the phosphonate ester intermediates 19 in which X is sulfur and X' is a direct bond.

- 5 Schemes 107 and 108 illustrate the preparation of the phosphonate esters 19 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the phenylalanine derivative 37.1 to afford the amide 107.1. The product is then converted, as described in Scheme 49, into the diamide 107.2.

- 10 The reactions shown in Scheme 107 illustrate the preparation of the compounds 107.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 108 depicts the conversion of the compounds 107.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 19 in which X is sulfur and X' is a direct

bond. In this procedure, the compounds **107.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **19**.

Preparation of the phosphonate ester intermediates 20 in which X and X' are direct bonds.

Schemes **109** and **110** illustrate the preparation of the phosphonate esters **20** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the tert. butylamine derivative **41.1** to afford the amide **109.1**. The product is then converted, as described in Scheme **49**, into the diamide **109.2**.

- 10 The reactions shown in Scheme **109** illustrate the preparation of the compounds **109.2** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme **110** depicts the conversion of the compounds **109.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X and X' are direct bonds. In this procedure, the compounds **109.2** are converted, using the procedures described below,
- 15 Schemes **133 - 197**, into the compounds **20**.

Preparation of the phosphonate ester intermediates 20 in which X is a direct bond and X' is sulfur.

- Schemes **111** and **112** illustrate the preparation of the phosphonate esters **20** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled, as described in Scheme **1**, with the amine **41.1** to afford the amide **111.1**. The product is then converted, as described in Scheme **49**, into the diamide **111.2**.

- The reactions shown in Scheme **111** illustrate the preparation of the compounds **111.2** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme **112** depicts the conversion of the compounds **111.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **111.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **20**.

Preparation of the phosphonate ester intermediates 20 in which X and X' are sulfur.

Schemes 113 and 114 illustrate the preparation of the phosphonate esters 20 in which X and X' are sulfur. As shown in Scheme 113, the carboxylic acid 80.2 is coupled, as described in Scheme 1, with the tert. butylamine derivative 41.1 to give the amide 113.1. The product is then transformed, as described in Scheme 49, into the diamide 113.2.

The reactions shown in Scheme 113 illustrate the preparation of the compounds 113.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 114 depicts the conversion of the compounds 113.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 20 in which X and X' are sulfur. In this procedure, the compounds 113.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 20.

Preparation of the phosphonate ester intermediates 20 in which X is sulfur and X' is a direct bond.

Schemes 115 and 116 illustrate the preparation of the phosphonate esters 20 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the tert. butylamine derivative 41.1 to afford the amide 115.1. The product is then converted, as described in Scheme 49, into the diamide 115.2.

The reactions shown in Scheme 115 illustrate the preparation of the compounds 115.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 116 depicts the conversion of the compounds 115.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 20 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 115.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 20.

Preparation of the phosphonate ester intermediates 21 in which X and X' are direct bonds.

Schemes 117 and 118 illustrate the preparation of the phosphonate esters 21 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in Scheme 1, with the decahydroisoquinoline derivative 45.1 to afford the amide 117.1. The product is then converted, as described in Scheme 49, into the diamide 117.2.

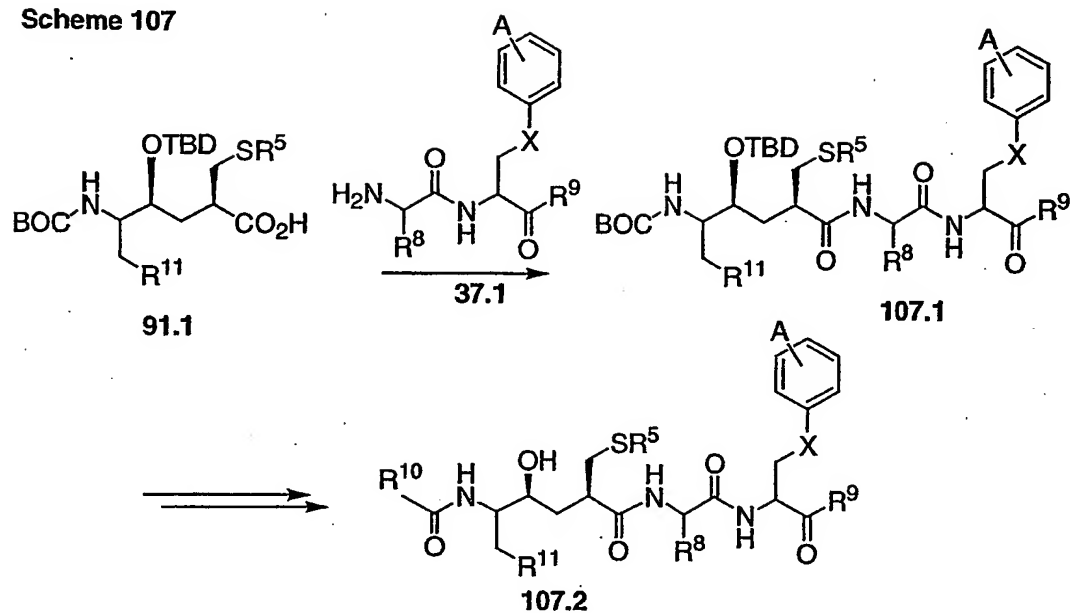
- 5 The reactions shown in Scheme 117 illustrate the preparation of the compounds 117.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 118 depicts the conversion of the compounds 117.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X and X' are direct bonds. In this procedure, the compounds 117.2 are converted, using the procedures described below,
- 10 Schemes 133 - 197, into the compounds 21.

Preparation of the phosphonate ester intermediates 21 in which X is a direct bond and X' is sulfur.

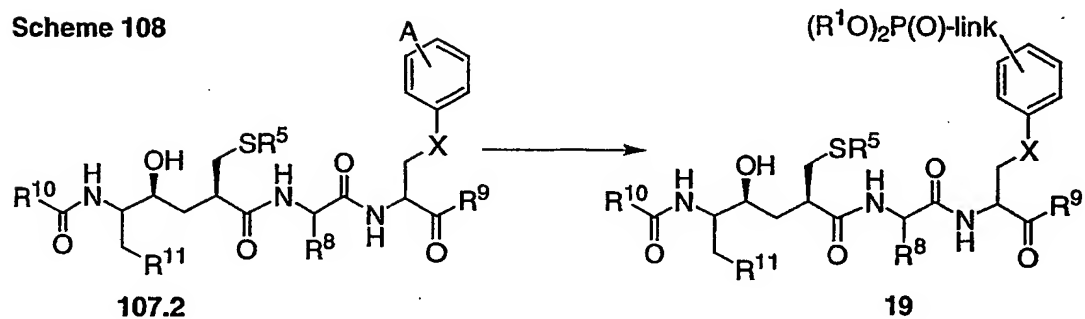
- Schemes 119 and 120 illustrate the preparation of the phosphonate esters 21 in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid 78.2 is coupled, as
- 15 described in Scheme 1, with the amine 45.1 to afford the amide 119.1. The product is then converted, as described in Scheme 49, into the diamide 119.2.

- The reactions shown in Scheme 119 illustrate the preparation of the compounds 119.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],
- 20 [SH], [NH], Br. Scheme 120 depicts the conversion of the compounds 119.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X is a direct bond and X' is sulfur. In this procedure, the compounds 119.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 21.

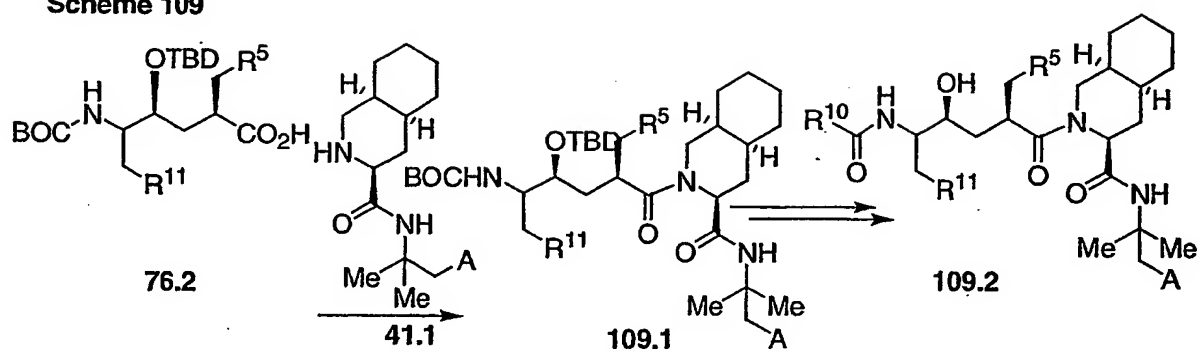
Scheme 107



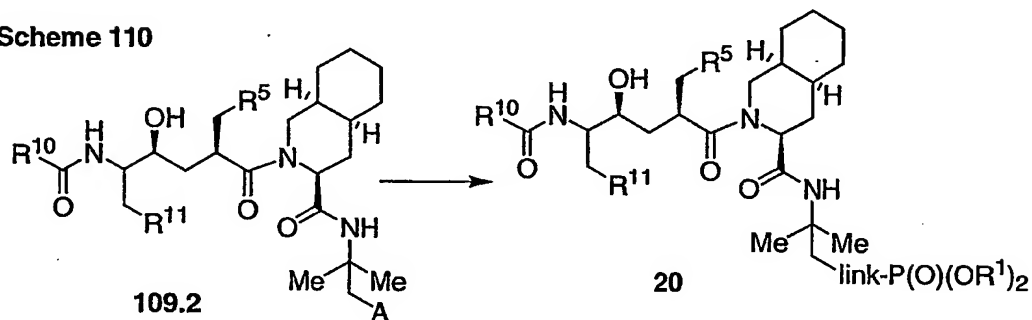
Scheme 108



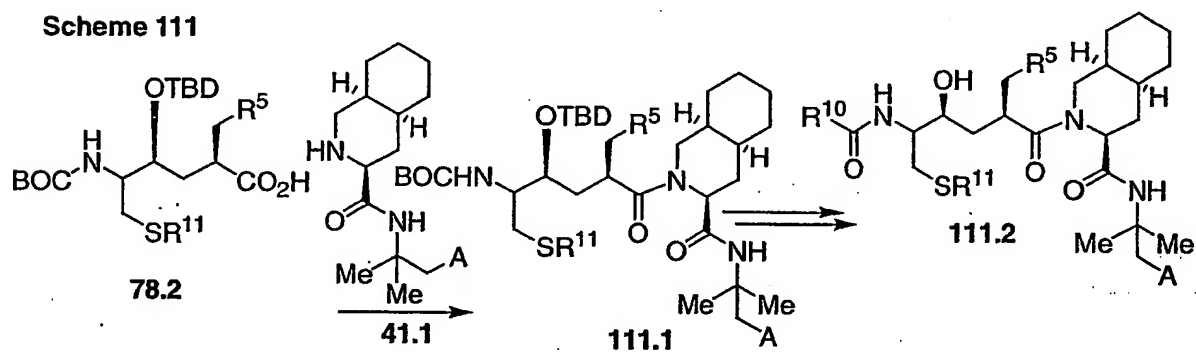
Scheme 109



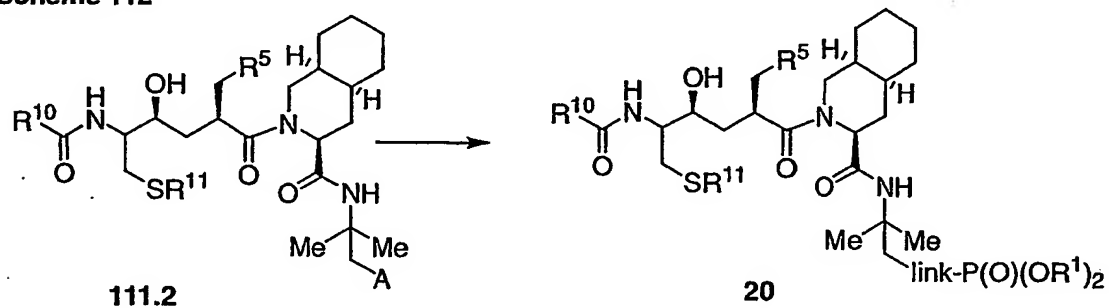
Scheme 110



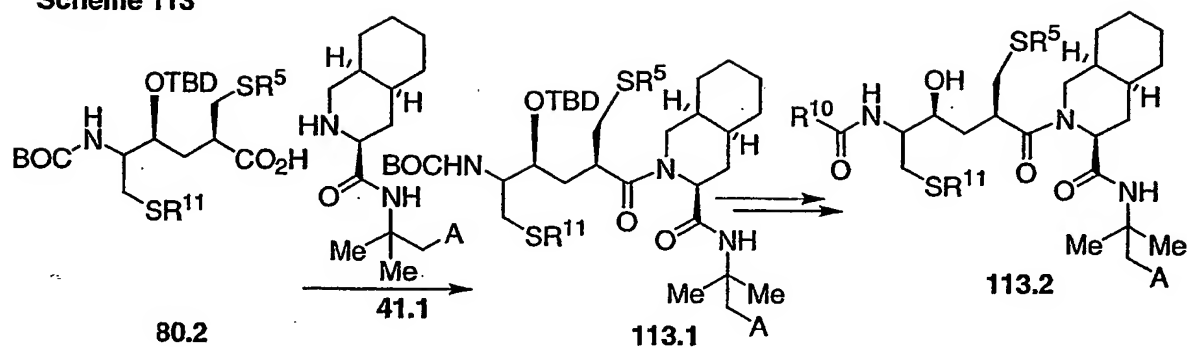
Scheme 111



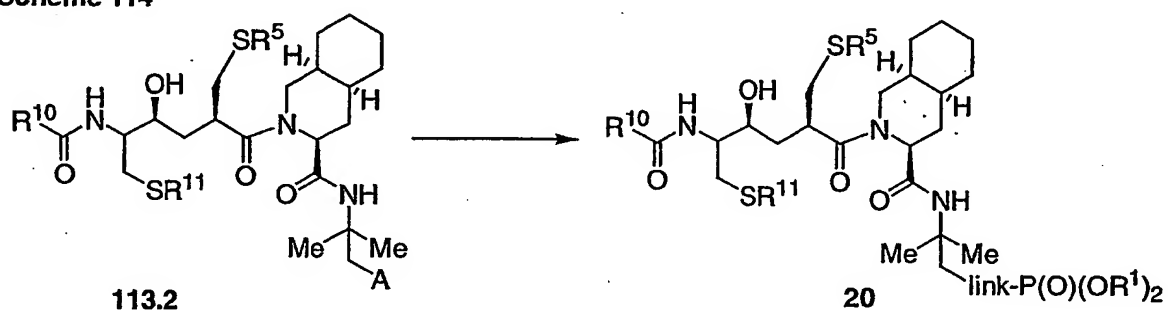
Scheme 112



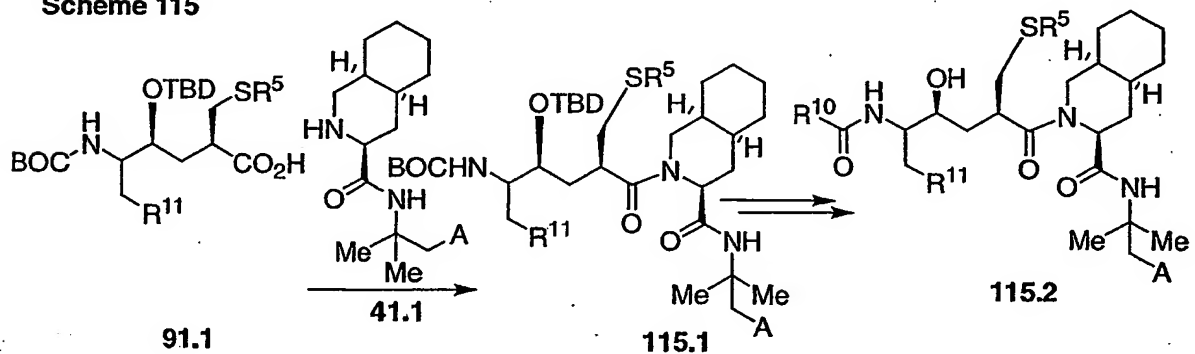
Scheme 113



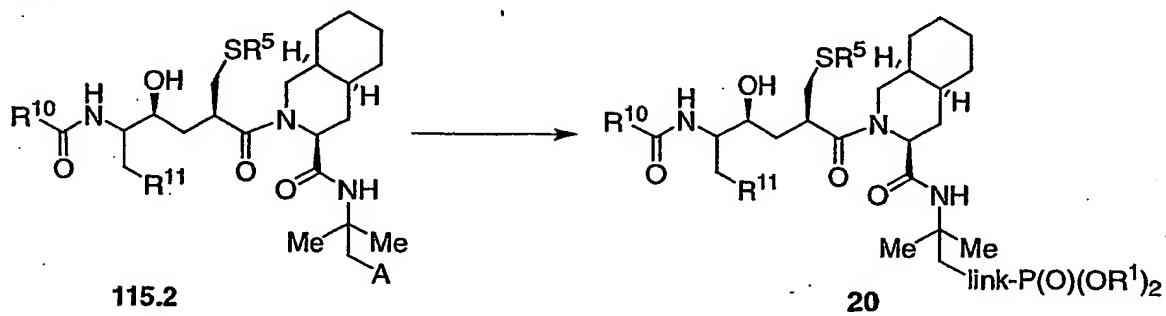
Scheme 114



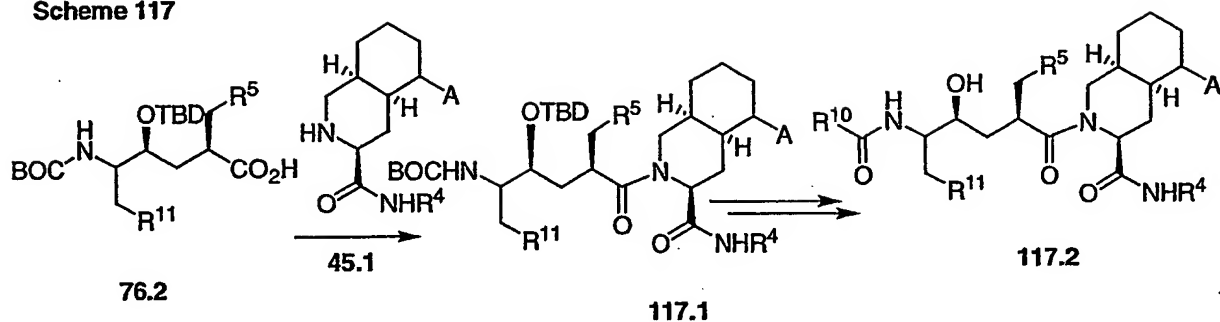
Scheme 115



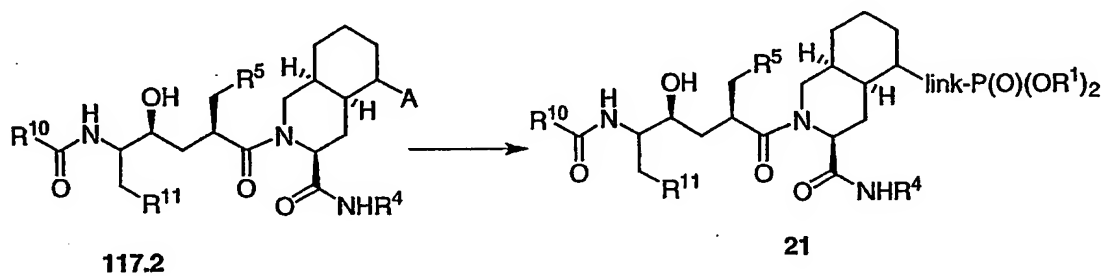
Scheme 116



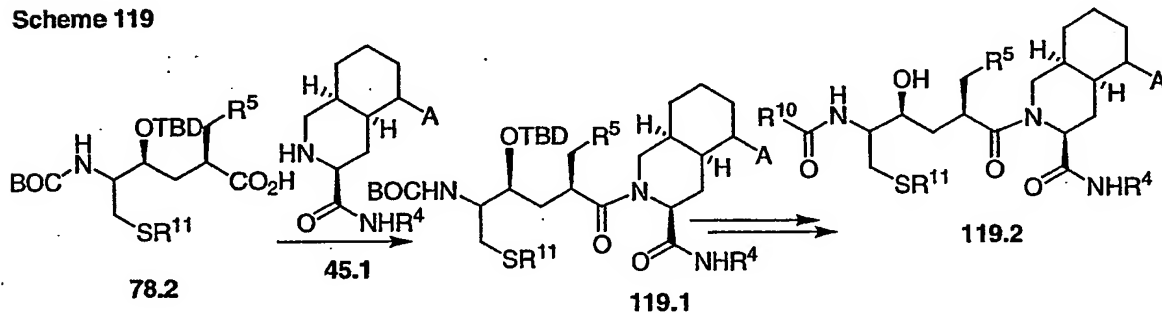
Scheme 117



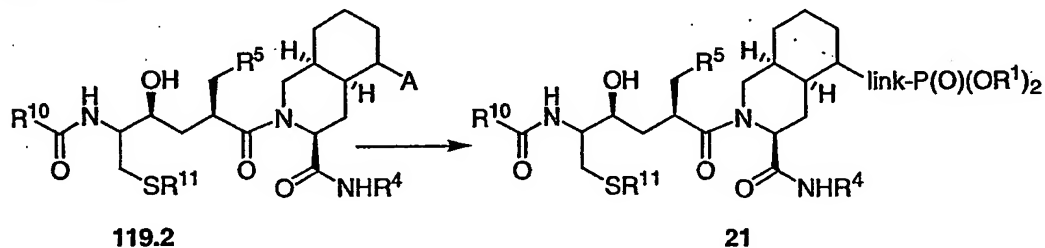
Scheme 118



Scheme 119



Scheme 120



Preparation of the phosphonate ester intermediates 21 in which X and X' are sulfur.

- 5 Schemes 121 and 122 illustrate the preparation of the phosphonate esters 21 in which X and X' are sulfur. As shown in Scheme 121, the carboxylic acid 80.2 is coupled with the amine

45.1 to give the amide 121.1. The product is then transformed, as described in Scheme 49, into the diamide 121.2.

The reactions shown in Scheme 121 illustrate the preparation of the compounds 121.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 122 depicts the conversion of the compounds 121.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X and X' are sulfur. In this procedure, the compounds 121.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 21.

10 Preparation of the phosphonate ester intermediates 21 in which X is sulfur and X' is a direct bond.

Schemes 123 and 124 illustrate the preparation of the phosphonate esters 21 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the amine 45.1 to afford the amide 123.1. The product is then converted, as described in Scheme 49, into the diamide 123.2.

The reactions shown in Schemes 123 illustrate the preparation of the compounds 123.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 124 depicts the conversion of the compounds 123.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 123.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 21.

Preparation of the phosphonate ester intermediates 22 in which X and X' are direct bonds.

Schemes 125 and 126 illustrate the preparation of the phosphonate esters 22 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in Scheme 5 with the amine 1.6, to afford the amide 125.1. The BOC protecting group is then removed, as described in Scheme 49, to yield the amine 125.2. The latter compound is then

coupled with the carboxylic acid 125.3 to produce the amide 125.4. The preparation of the carboxylic acid reactant 125.3 is described in Scheme 191.

The reactions shown in Scheme 125 illustrate the preparation of the compounds 125.4 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 126 depicts the conversion of the compounds 125.4 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22 in which X and X' are direct bonds. In this procedure, the compounds 125.4 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 22

10 Preparation of the phosphonate ester intermediates 22 in which X is a direct bond and X' is sulfur.

Schemes 127 and 128 illustrate the preparation of the phosphonate esters 22 in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid 78.2 is coupled, as described in Scheme 5 with the amine 1.6, to afford the amide 127.1. The BOC protecting group is then removed, as described in Scheme 49, to yield the amine 127.2. The latter compound is then coupled, as described in Scheme 1, with the carboxylic acid 125.3 to produce the amide 127.3.

The reactions shown in Scheme 127 illustrate the preparation of the compounds 127.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 128 depicts the conversion of the compounds 127.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22, in which X is a direct bond and X' is sulfur. In this procedure, the compounds 127.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 22.

25 Preparation of the phosphonate ester intermediates 22 in which X and X' are sulfur.

Schemes 129 and 130 illustrate the preparation of the phosphonate esters 22 in which X and X' are sulfur. As shown in Scheme 129, the carboxylic acid 80.2 is coupled, as described in Scheme 5, with the amine 1.6, to afford the amide 129.1. The BOC protecting group is then

removed, as described in Scheme 49, to yield the amine 129.2. The latter compound is then coupled, as described in Scheme 1, with the carboxylic acid 125.3 to produce the amide 129.3.

The reactions shown in Scheme 129 illustrate the preparation of the compounds 129.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],

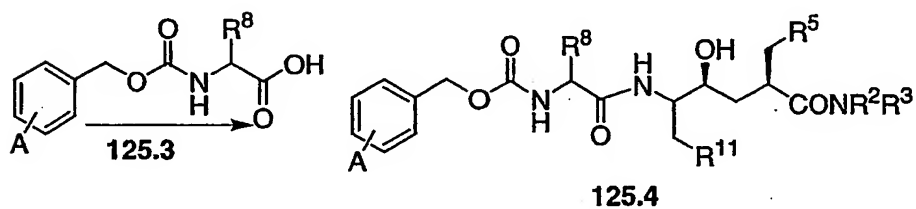
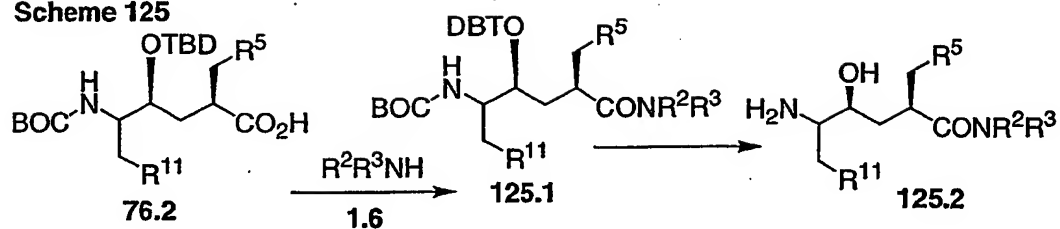
- 5 [SH], [NH], Br. Scheme 130 depicts the conversion of the compounds 129.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22, in which X and X' are sulfur. In this procedure, the compounds 129.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 22.

- 10 **Preparation of the phosphonate ester intermediates 22 in which X is sulfur and X' is a direct bond.**

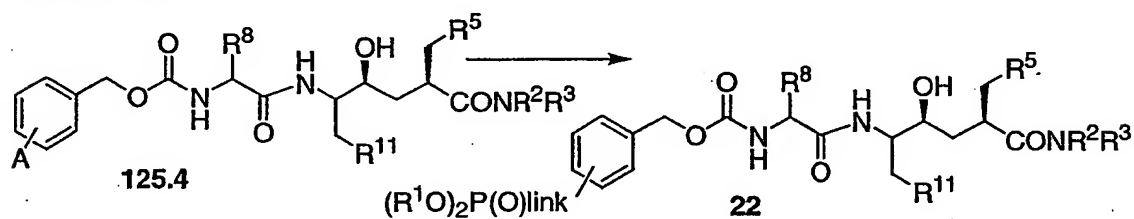
- Schemes 131 and 132 illustrate the preparation of the phosphonate esters 22 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 5, with the amine 1.6, to afford the amide 131.1. The BOC protecting
15 group is then removed, as described in Scheme 49, to yield the amine 131.2. The latter compound is then coupled, as described in Scheme 1, with the carboxylic acid 125.3 to produce the amide 131.3.

- The reactions shown in Scheme 131 illustrate the preparation of the compounds 131.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],
20 [SH], [NH], Br. Scheme 132 depicts the conversion of the compounds 131.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 131.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 22.

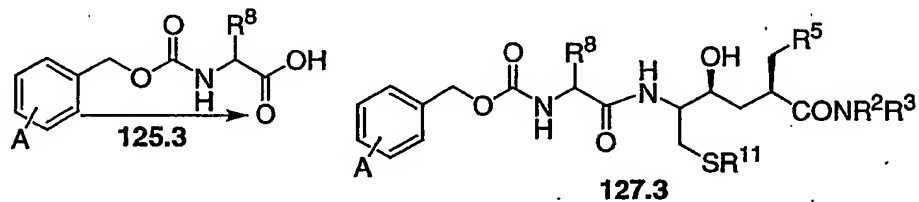
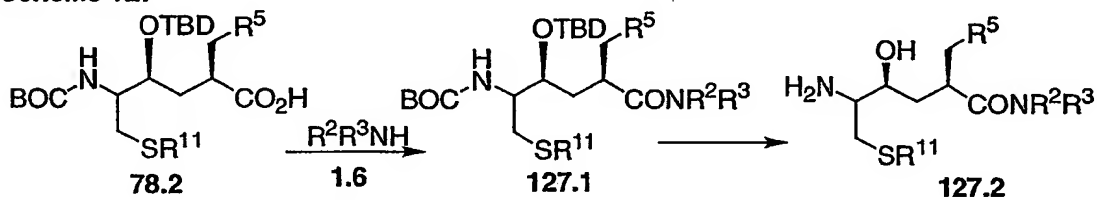
Scheme 125



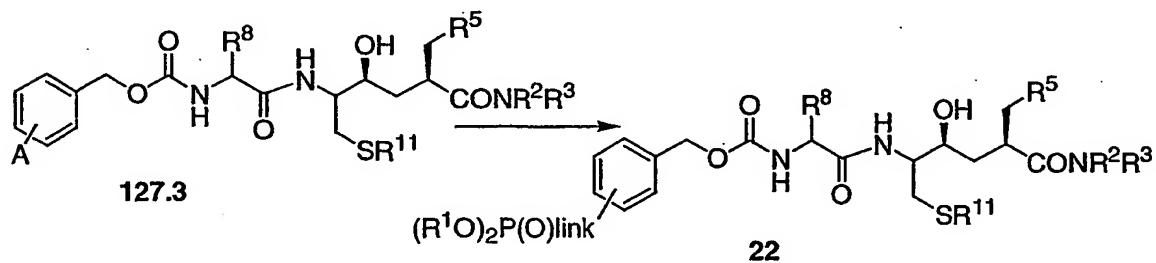
Scheme 126



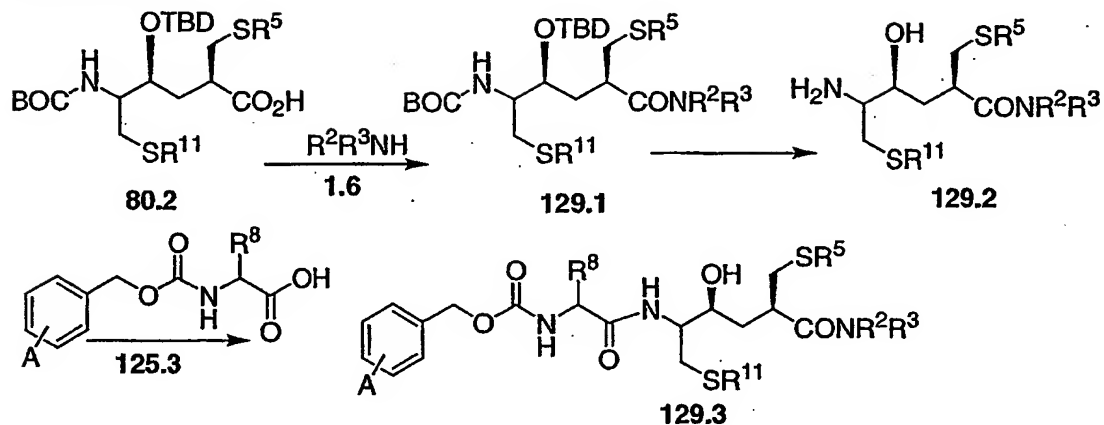
Scheme 127



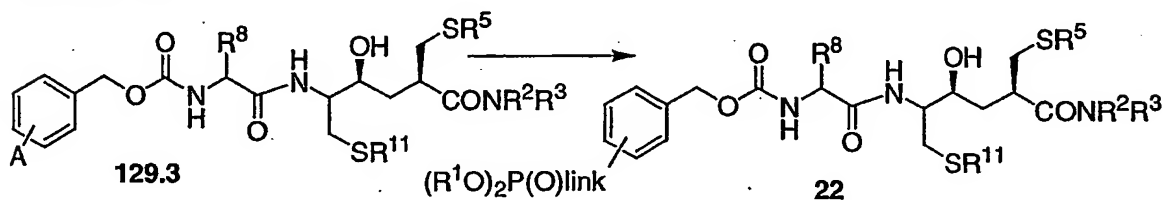
Scheme 128



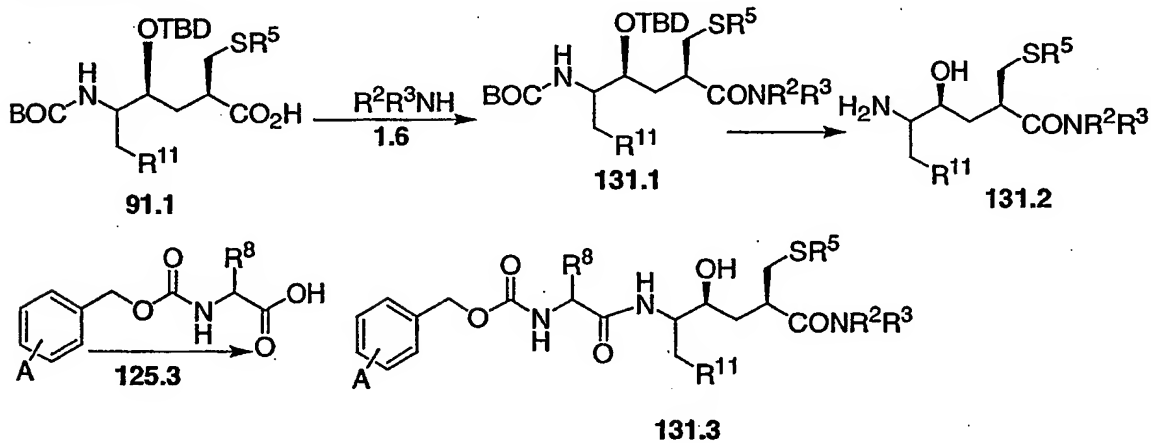
Scheme 129



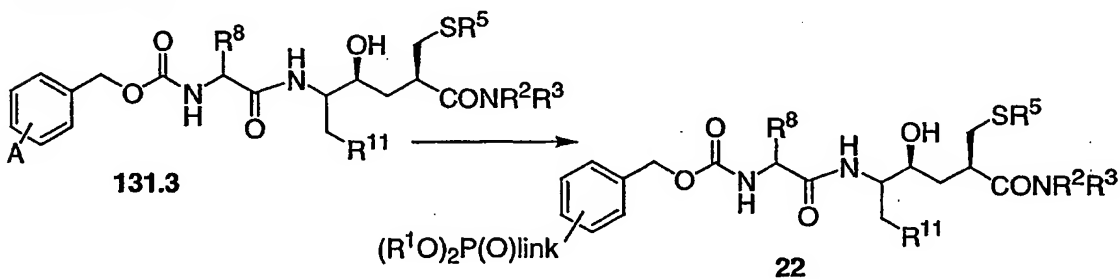
Scheme 130



Scheme 131



Scheme 132



Preparation of aminoindanol derivatives 1.2 incorporating phosphonate moieties.

Scheme 133 illustrates the preparation of variously substituted derivatives of 3-amino-indan-1,2-diol, the preparation of which is described in J. Med. Chem., 1991, 34, 1228. The
5 alcohols, thiols, amines and bromo compounds shown in Scheme 133 can then be transformed into phosphonate-containing reactants 1.2, as described below, (Schemes 134 - 137). The reactants 1.2 are employed in the preparation of the phosphonate esters 1 and 16.

In order to effect changes to the 1-substituent, the starting material 133.1 is transformed into the protected compound 133.2. For example, the aminoalcohol 133.1 is treated with 2-
10 methoxypropene in the presence of an acid catalyst, such as p-toluenesulfonic acid, in a solvent such as tetrahydrofuran, as described in WO9628439, to afford the acetonide-protected product 133.2.

The amino group present in 133.2 is protected to afford the intermediate 133.3, in which R¹² is a protecting group, stable to the subsequent reactions. For example, R¹² can be
15 carbobenzyloxy (cbz), tert-butoxycarbonyl (BOC) and the like, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309.

The free hydroxyl group present in the N-protected acetonide 133.3 is then converted into a suitable leaving group, such as, for example, trifluoromethylsulfonyloxy, p-toluenesulfonyloxy
20 or, preferably, methanesulfonyloxy. This transformation is effected by treatment of 133.3 with a slight molar excess of the corresponding acid chloride or anhydride, in the presence of an organic base.

For example, treatment of 133.3 with methanesulfonyl chloride and pyridine in dichloromethane at ambient temperature affords the mesylate 133.4.

25 The α -mesylate group in the product 133.4 is then subjected to displacement reactions with nitrogen, sulfur or oxygen nucleophiles, to effect introduction of the various heteroatoms with inversion of stereochemistry.

For example, the mesylate 133.4 is reacted with a nitrogen nucleophile such as potassium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic
30 Transformations, by R. C. Larock, VCH, p. 399, to afford the amine 133.9.

Preferably, the mesylate 133.4 is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such

as, for example, dimethylformamide, at ambient temperature, to afford the displacement product 133.5, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the β -amine 133.9.

5 The mesylate 133.4 is treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate group, followed by mild basic hydrolysis, for example by treatment with aqueous sodium bicarbonate or aqueous ammonia, to afford the β -thiol 133.12.

10 Preferably, the mesylate 133.4 is reacted with one molar equivalent of potassium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate 133.8. The product then treated with a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the β -thiol 133.12.

15 The mesylate 133.4 is transformed into the β -carbinol 133.7, by treatment with an oxygen nucleophile. Conversion of sulfonate esters and related compounds to the corresponding carbinols is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 481. For example, the mesylate can be reacted with potassium superoxide, in the presence of a crown ether such as 18-crown-6, as described in Tet. Lett., 3183, 1975, to
20 afford the β -carbinol 133.7.

The carbinol 133.3 is also transformed into the β -bromo compound 133.6. Methods for the conversion of carbinols to bromo compounds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 356.

For example, the α -carbinol 133.3 is reacted with hexabromoethane and triphenylphosphine, in
25 an aprotic solvent such as ethyl acetate, as described in Syn., 139, 1983, to afford the β -bromo compound 133.6.

Using the above described procedures for the conversion of the α -carbinol 133.3 into the β -oriented amine 133.9, thiol 133.12 and bromo compound 133.6, the β -carbinol 133.7 is transformed into the α -oriented amine or thiol 133.11 or the bromo compound 133.10.

30

Schemes 134 - 137 illustrate the preparation of aminoindanol derivatives incorporating the group link-P(O)(OR¹)₂, derived from the intermediates whose syntheses are described above (Scheme 133).

- 5 Scheme 134 depicts the preparation of phosphonate esters linked to the aminoindanol nucleus by means of a carbon chain and a heteroatom O, S or N. In this procedure, the hetero-substituted indanol 134.1 is reacted with a bromoalkylphosphonate 134.2, in the presence of a suitable base. The base required for this transformation depends on the nature of the heteroatom X. For example, if X is N or S, an excess of an inorganic base such as, for
- 10 example, potassium carbonate, in the presence of an organic solvent such as dimethylformamide, is suitable. The reaction proceeds at from ambient temperature to about 80°C to afford the displacement products 134.3. If X is O, an equimolar amount of a strong base, such as, for example, lithium hexamethyldisilylazide and the like, is employed, in the presence of a solvent such as tetrahydrofuran. Deprotection, by removal of the group R¹²,
- 15 then affords the amine 134.4.
- For example, the β-thiol 133.12 is reacted with an equimolar amount of dialkyl 4-bromobutyl phosphonate 134.5, the preparation of which is described in Synthesis, 1999, 9, 909, in dimethylformamide containing excess potassium carbonate, at ca 60°C to afford the thioether phosphonate product 134.6. Deprotection then affords the amine 134.7.
- 20 Using the above procedures, but employing, in place of the thiol 133.12, different carbinols, thiols or amines 134.1, and/or different bromoalkylphosphonates 134.2, the corresponding products 134.4 are obtained.

- Scheme 135 illustrates the preparation of aminoindanol derivatives in which the phosphonate ester group is attached by means of a nitrogen atom and a carbon chain. In this method, the aminoindanol 135.1 is reacted with a formyl-substituted phosphonate ester, utilizing a
- 25 reductive amination procedure. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component 135.1 and the aldehyde
- 30 component 135.2 are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product 135.3. Deprotection, by removal of the R¹² group, then affords the amine 135.4.

For example, equimolar amounts of the amine 133.11 and a dialkylformylphosphonate 135.5, prepared as described in US 3784590, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in J. Am. Chem. Soc., 91, 3996, 1969, to afford the product 135.6 which is then deprotected to produce the amine 135.7.

- 5 Using the above procedures, but employing, in place of the α -amine 133.11, the β -amine 133.9, and/or different formyl-substituted phosphonates 135.2, the corresponding products 135.4 are obtained.

Scheme 136 depicts the preparation of aminoindanol phosphonates in which the phosphonate moiety is attached to the nucleus by means of a heteroatom and one carbon. In this procedure, a carbinol, thiol or amine 136.1 is reacted with a dialkyl trifluoromethylsulfonyloxy phosphonate 136.2, in the presence of a suitable base, to afford the alkylation product 136.3. Deprotection of the product 136.3 then yields the amine 136.4. The base required for this reaction between 136.1 and 136.2 depends on the nature of the heteroatom X. For example, if X is N or S, an excess of inorganic base such as, for example, potassium carbonate, cesium carbonate or the like, in the presence of an organic solvent such as dimethylformamide, is suitable. The reaction proceeds at from ambient temperature to about 80° to afford the displacement products 136.3. If X is O, an equimolar amount of a strong base, such as, for example, lithium hexamethyldisilylazide, sodium hydride or the like, is employed, in the presence of a solvent such as tetrahydrofuran.

For example, the α -carbinol 133.3 is reacted with one equivalent of lithium hexamethyl disilylazide in tetrahydrofuran, followed by addition of an equimolar amount of a dialkyl trifluoromethylsulfonyloxymethyl phosphonate 136.5, the preparation of which is described in Tet. Lett., 1986, 27, 1497, to afford the ether product 136.6. Deprotection, by removal of the R¹² group, then affords the amine 136.7.

Using the above procedures, but employing, in place of the α -carbinol 133.3, different carbinols, thiols or amines 136.1, and /or different dialkyl trifluoromethylsulfonyloxymethyl phosphonates 136.2, the corresponding products 136.4 are obtained.

30 Scheme 137 illustrates the preparation of aminoindanol phosphonate esters in which the phosphonate group is attached directly to the aminoindanol nucleus.

In this procedure, the bromoindanol derivative **137.1** is reacted with a sodium dialkyl phosphite, in a suitable aprotic polar solvent such as dimethyl formamide or N-methylpyrrolidinone. Displacement of the bromo substituent occurs to yield the phosphonate **137.3**. Deprotection, by removal of the R¹² group, then affords the amine **137.4**.

5 For example, equimolar amounts of the α -bromo compound **133.10** and the dialkyl sodium phosphite **137.2**, are dissolved in dimethylformamide and the mixture is heated at ca. 60°C, as described in J. Med. Chem., 35, 1371, 1992, to afford the β -phosphonate **137.5**.

Alternatively, the phosphonate compound **137.5** is obtained by means of an Arbuzov reaction between the bromo compound **133.10** and a trialkyl phosphite P(OR¹)₃. In this procedure, as
10 described in Handb. Organophosphorus Chem., 1992, 115, the reactants are heated together at ca. 100°C to afford the product **137.5**. Deprotection of the latter compound affords the amine **137.6**.

Using the above procedures, but employing, in place of the α -bromo compound **133.10**, the β -bromo compound **133.6**, and/or different phosphites **137.2**, the corresponding phosphonates
15 **137.4** are obtained.

Preparation of phenylpropionic acid intermediates 5.1 incorporating phosphonate moieties.

20 Phenylpropionic acid derivatives incorporating the substituent link-P(O)(OR¹)₂ are prepared by the reactions illustrated in Schemes **139-143**, using as starting materials variously substituted phenylpropionic acids. The phenylpropionic acid derivatives **5.1** are employed in the preparation of the phosphonate esters **2** in which X is a direct bond.

A number of the substituted phenylpropionic acids required for the reactions shown in
25 Schemes **139-143** are commercially available; in addition, the syntheses of variously substituted phenylpropionic acids have been reported. For those substituted phenylpropionic acids which are not commercially available, and whose syntheses have not been reported, a number of well-established synthetic routes are available. Representative methods for the synthesis of substituted phenylpropionic acids from commercially available starting materials
30 are shown in Scheme **138**.

For example, variously substituted benzaldehydes **138.1** are subjected to a Wittig reaction with carboethoxymethylenetriphenylphosphorane **138.2**, as described in Ylid Chemistry, by A. W.

Johnson, Academic Press, 1966, p. 132, to afford the corresponding cinnamate esters **138.3**. Equimolar amounts of the reactants **138.1** and **138.2** are heated in an inert solvent such as dioxan or dimethylformamide, at ca 50°C, to afford the product **138.3**. Reduction of the double bond in the product **138.3** then afford the saturated ester **138.6**, (X =H) which upon

5 hydrolysis yields the phenylpropionic acid intermediate **138.10**.

Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 6. Typical of the available reduction methods are catalytic hydrogenation, for example using palladium catalysts, as described in Hydrogenation Methods, by P. N. Rylander, Academic Press, New

10 York, 1985, hydroboration-protonolysis, as described in J. Am. Chem. Soc., 81, 4108, 1959, or diimide reduction, as described in J. Org. Chem., 52, 4665, 1987. The choice of a particular reduction method is made by one skilled in the art, depending on the nature of the substituent groups attached to the cinnamic acid ester **138.3**.

Alternatively, the cinnamic esters **138.3** are obtained by means of a palladium-catalyzed Heck

15 reaction between an appropriately substituted bromobenzene **138.5** and ethyl acrylate **138.4**. In this procedure, a substituted bromobenzene **138.5** is reacted with ethyl acrylate in the presence of a palladium (II) catalyst, as described in J. Med. Chem., 35, 1371, 1992, to afford the cinnamate ester **138.3**. Equimolar amounts of the reactants **138.4** and **138.5** are dissolved in a polar aprotic solvent such as dimethylformamide or tetrahydrofuran, at a temperature of

20 about 60°C, in the presence or ca. 3 mol % of, for example, bis(triphenylphosphine)palladium (II) chloride and triethylamine, to afford the product **138.3**.

Alternatively, the substituted phenylpropionic acid intermediates are obtained from the correspondingly substituted methylbenzenes **138.7**. In this procedure, the methylbenzene **138.7** is subjected to free-radical bromination, for example by reaction with an equimolar

25 amount of N-bromosuccinimide, as described in Chem. Rev., 63, 21, 1963, to afford the bromomethyl derivative **138.8**. The latter compound is then reacted with a salt of an ester of malonic acid, for example the sodium salt of diethyl malonate **138.9**, as described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 489, to afford the displacement product **138.6**, (X = COOEt). The latter compound is subjected to hydrolysis

30 and decarboxylation, for example by treatment with aqueous alkali or dilute aqueous acid, to afford the phenylpropionic acid **138.10**.

Scheme 139 illustrates the preparation of phosphonate-containing phenylpropionic acids in which the phosphonate moiety is attached to the phenyl ring by means of an aromatic group. In this procedure, the carboxyl group of a bromo-substituted phenylpropionic acid 139.1 is protected. Methods for the protection of carboxylic acids are described, for example, in

5 Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224. The product 139.2 is then subjected to halogen-methyl exchange, for example by reaction with an alkyl lithium, to afford the product 139.3 in which M is Li. The latter compound is subjected to palladium (II) or palladium (0) catalyzed coupling, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57.

10 Compound 139.3 is first converted into the boronic acid 139.4, by reaction with a trialkyl borate, and the boronic acid product is coupled with a dialkyl bromophenylphosphonate 139.5 to yield the product 139.6. Deprotection then affords the intermediate phosphonate-substituted phenylpropionic acid 139.7.

For example, 4-bromophenylpropionic acid 139.8, prepared as described in U.S. 4,032,533, is
15 converted into the acid chloride, by treatment with thionyl chloride, oxalyl chloride and the like. The acid chloride is then reacted with 3-methyl-3-oxetanemethanol 139.9 (Aldrich), in the presence of a tertiary organic base such as pyridine, in a solvent such as dichloromethane, to afford the ester 139.10. This product is then rearranged by treatment with boron trifluoride etherate in dichloromethane, at about -15°C as described in Protective Groups in Organic

20 Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 268, to yield the orthoester 139.11, known as an OBO ester. The latter product is then reacted with one molar equivalent of n-butyllithium, in a solvent such as ether, at about -80°C, to afford the lithio derivative, which is reacted with a trialkyl borate, as described in J. Organomet. Chem., 1999, 581, 82, to yield the boronate 139.12. This material is coupled, in the presence of a catalytic

25 amount of tetrakis(triphenylphosphine)palladium(0), and an inorganic base such as sodium carbonate, with a dialkyl 4-bromophenylphosphonate 139.13, prepared as described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, to give the coupled product 139.14. Deprotection, for example by treatment with aqueous pyridine p-toluenesulfonate, as described in Can. J. Chem., 61, 712, 1983, then affords the carboxylic acid 139.15.

30 Using the above procedures, but employing, in place of the 4-bromophenylpropionic acid 139.8, different bromophenylpropionic acids 139.1, and/or different dialkyl bromophenyl phosphonates 139.5, the corresponding products 139.7 are obtained.

Scheme 140 depicts the preparation of phenylpropionic acids in which a phosphonate ester is attached to the phenyl ring by means of a heteroatom. In this procedure, a suitably protected hydroxy, thio or amino-substituted phenyl propionic acid 140.1 is reacted with a derivative of
5 a hydroxymethyl dialkylphosphonate 140.2, in which Lv is a leaving group such as methanesulfonyloxy and the like. The reaction is conducted in a polar aprotic solvent, in the presence of an organic or inorganic base, to afford the displacement product 140.3.

Deprotection then affords the carboxylic acid 140.4.

For example, trichloroethyl 3-hydroxyphenylpropionic acid 140.5, prepared by reaction of 3-
10 hydroxyphenylpropionic acid (Fluka) with trichloroethanol and dicyclohexylcarbodiimide, as described in J. Am. Chem. Soc., 88, 852, 1966, is reacted with a dialkyl

trifluoromethanesulfonyloxymethyl phosphonate 140.6, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product 140.7. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide, in the presence of a base such as

15 potassium carbonate, at about 50°C, to afford the product 140.7. Removal of the trichloroethyl ester group, for example by treatment with zinc in acetic acid at 0°C, as described in J. Am. Chem. Soc., 88, 852, 1966, then yields the carboxylic acid 140.8.

Using the above procedures, but employing, in place of the phenol 140.5, different phenols, thiols or amines 140.1, and/or different phosphonates 140.2, the corresponding products 140.4
20 are obtained.

Scheme 141 illustrates the preparation of phenylpropionic acids in which a phosphonate moiety is attached by means of a chain incorporating a heteroatom. In this procedure, a carboxyl protected halomethyl substituted phenylpropionic acid 141.1 is reacted with a dialkyl
25 hydroxy, thio or amino-substituted alkylphosphonate 141.2. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant 141.2. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate
30 and the like is employed.

For example, 4-bromomethyl phenylpropionic acid, prepared as described in U.S. 4,032,533, is converted into the methoxymethyl ester 141.5, by reaction with methoxymethyl chloride and

triethylamine in dimethylformamide, as described in J. Chem. Soc, 2127, 1965. Equimolar amounts of the ester **141.5** and a dialkyl 2-aminoethyl phosphonate **141.6**, prepared as described in J. Org. Chem., 2000, 65, 676, are reacted in dimethylformamide at ca 80°C, in the presence of potassium carbonate, to afford the displacement product **141.7**. Deprotection, for example by treatment with trimethylsilyl bromide and a trace of methanol, as described in Aldrichimica Acta, 11, 23, 1978, then yields the carboxylic acid **141.8**.

Using the above procedures, but employing, in place of the amine **141.6**, different amines, alcohols or thiols **141.2** and/or different halomethyl-substituted phenylpropionic acids **141.1**, the corresponding products **141.4** are obtained.

Scheme **142** illustrates the preparation of phosphonate esters attached to the phenyl ring by means of an oxygen or sulfur link, by means of a Mitsunobu reaction. In this procedure, a protected hydroxy- or thio-substituted phenylpropionic acid **142.1** is reacted with a dialkyl hydroxyalkyl phosphonate **142.2**. The condensation reaction between **142.1** and **142.2** is effected in the presence of a triaryl phosphine and diethyl azodicarboxylate, as described in Org. React., 1992, 42, 335. The product **142.3** is then deprotected to afford the carboxylic acid **142.4**.

For example, 3-mercaptophenylpropionic acid (Apin Chemicals) is converted into the tert. butyl ester **142.5**, by treatment with carbonyl diimidazole, tert. butanol and

diazabicycloundecene, as described in Synthesis, 833, 1982. The ester is reacted with a dialkyl hydroxymethylphosphonate **142.6**, prepared as described in Synthesis, 4, 327, 1998, in the presence of triphenyl phosphine, triethylamine and diethyl azodicarboxylate, to afford the thioether **142.7**. The tert. butyl group is removed by treatment with formic acid at ambient temperature, as described in J. Org. Chem., 42, 3972, 1977, to yield the carboxylic acid **142.8**.

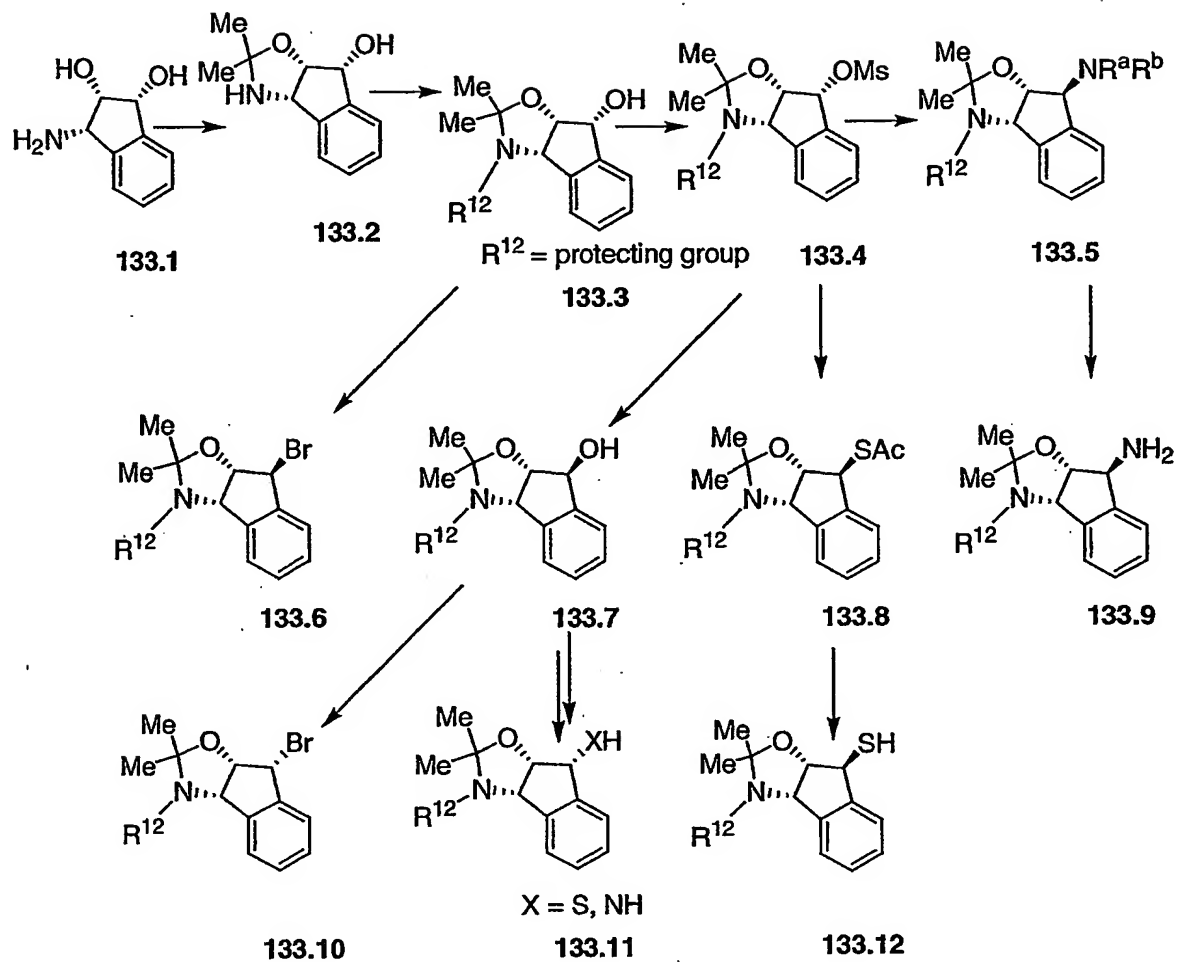
Using the above procedures, but employing, in place of the thiol **142.5**, different phenols or thiols **142.1** and/or different hydroxyalkyl phosphonates **142.2**, the corresponding products **142.4** are obtained.

Scheme **143** depicts the preparation of phenylpropionic acids linked to a phosphonate ester by means of an aromatic or heteroaromatic ring. The products **143.3** are obtained by means of an alkylation reaction in which a bromomethyl aryl or heteroaryl phosphonate **143.1** is reacted with a carboxyl-protected hydroxy, thio or amino-substituted phenylpropionic acid **140.1**. The

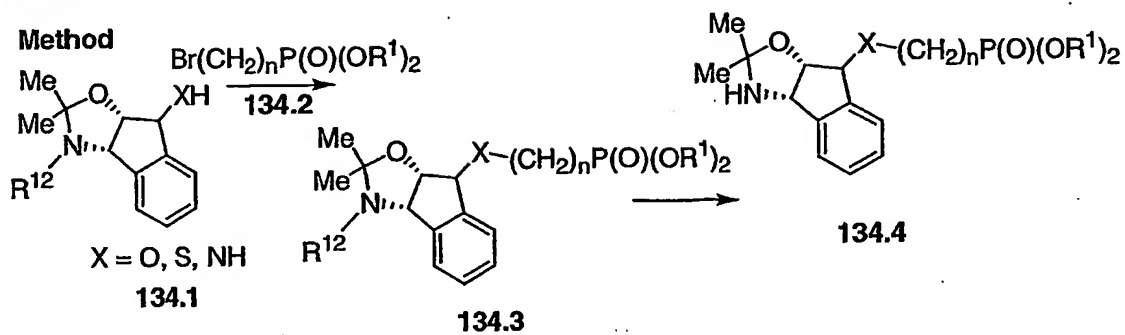
reaction is conducted in the presence of a base, the nature of which is determined by the substituent X in the reactant **140.1**. For example, if X is O, a strong base such as lithium hexamethyldisilylazide or sodium hydride is employed. If X is S or N, an organic or inorganic base, such as diisopropylethylamine or cesium carbonate is employed. The alkylated product **143.2** is then deprotected to afford the carboxylic acid **143.3**.

- For example, 3-(4-aminophenyl)propionic acid (Aldrich) is reacted with tert. butyl chlorodimethylsilane and imidazole in dimethylformamide, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 262, to afford the silyl ester **143.4**. This compound is reacted with a an equimolar amount of a dialkyl 4-bromomethylbenzylphosphonate **143.5**, prepared as described in Tet. Lett., 1998, 54, 9341, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the product **143.6**. The silyl ester is removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to give the carboxylic acid **143.7**.
- Using the above procedures, but employing, in place of the amino compound **143.4**, different phenols, mercaptans or amines **140.1**, and/or different halomethyl phosphonates **143.1**, the corresponding products **143.3** are obtained.

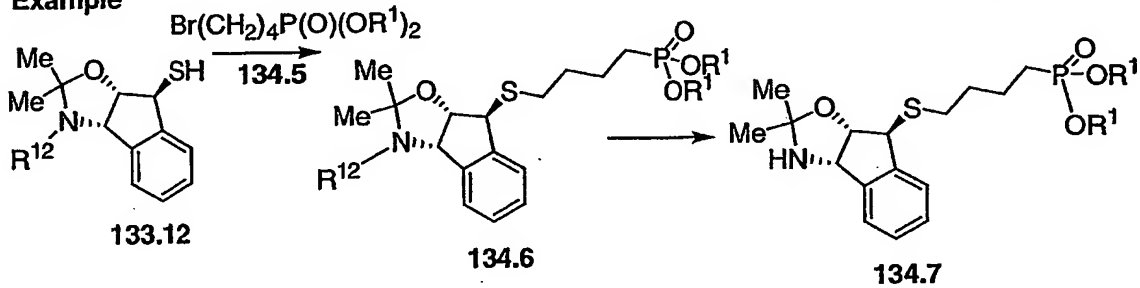
Scheme 133



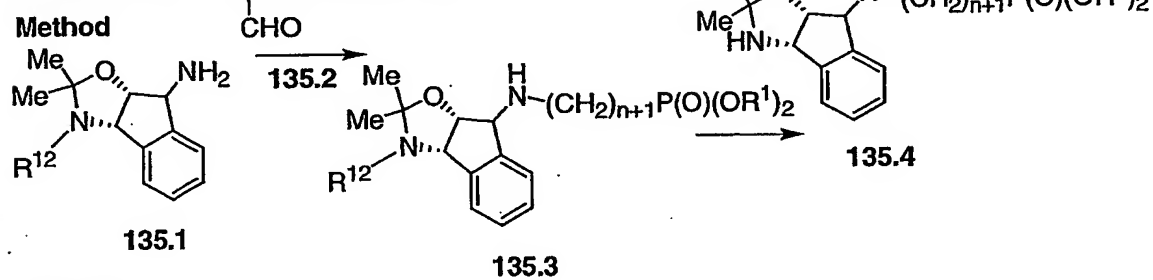
Scheme 134



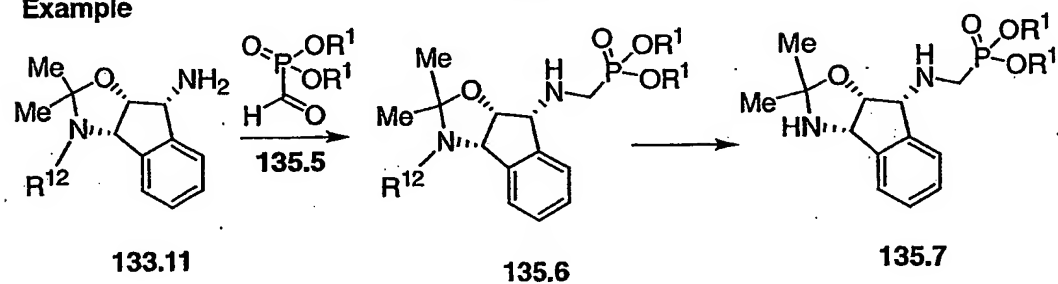
Example

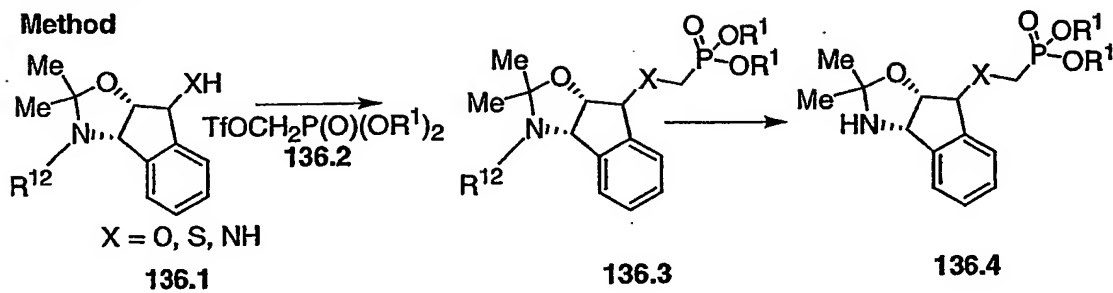
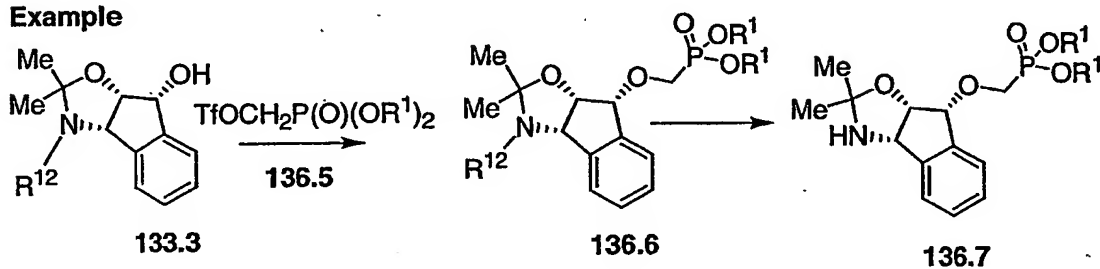
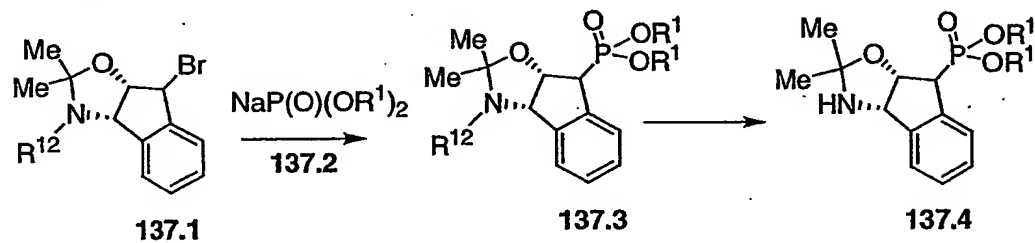
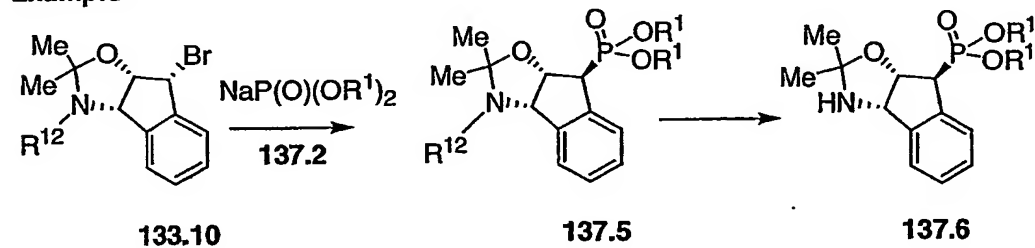


Scheme 135

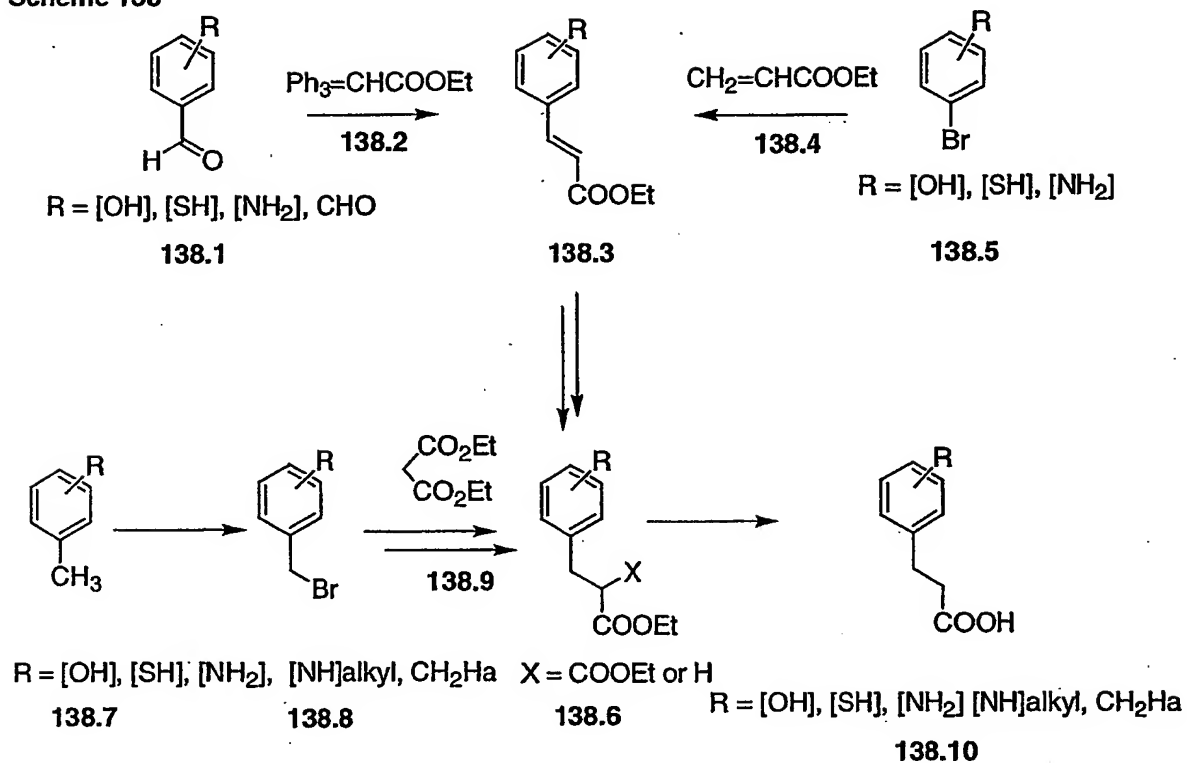


Example



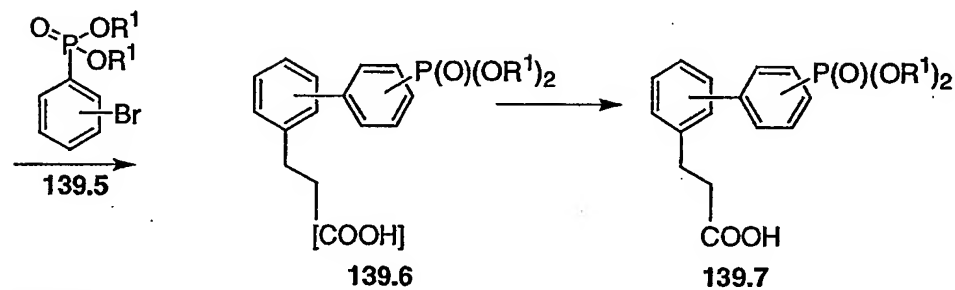
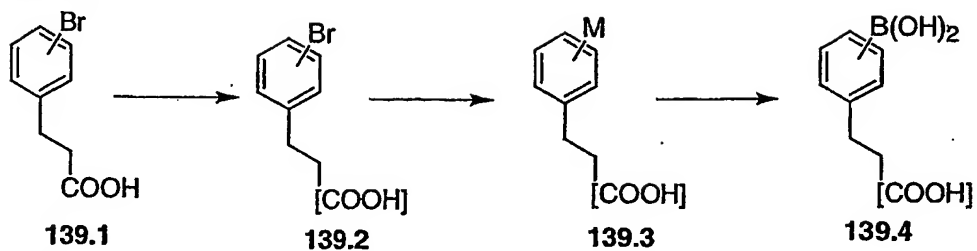
Scheme 136**Method****Example****Scheme 137****Method****Example**

Scheme 138

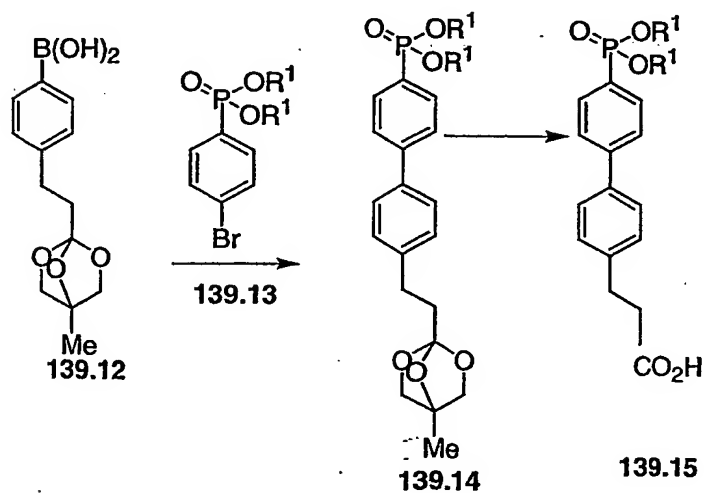
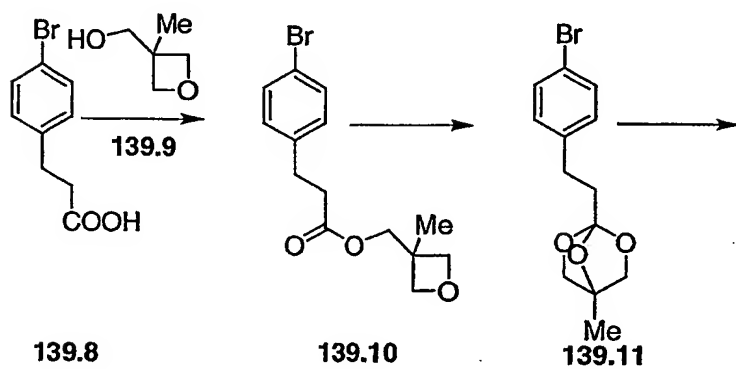


Scheme 139

Method



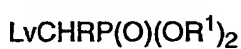
Example



Scheme 140

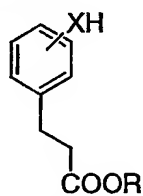
Method

R = H or alkyl

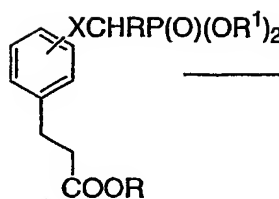


Lv = leaving group
140.2

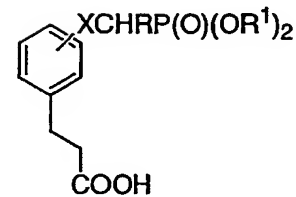
X = O, S, NH, Nalkyl



140.1

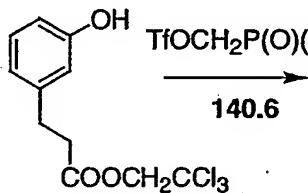


140.3

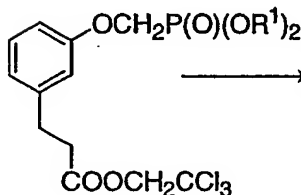
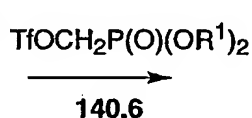


140.4

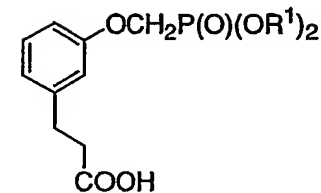
Example



140.5



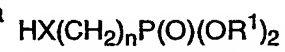
140.7



140.8

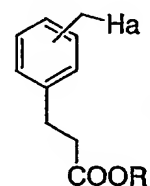
Scheme 141

Method

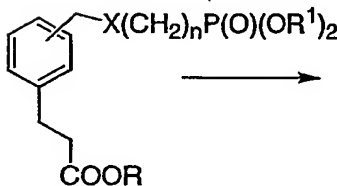


X = O, S, NH, Nalkyl

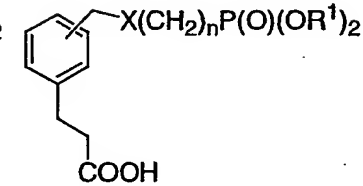
141.2



141.1

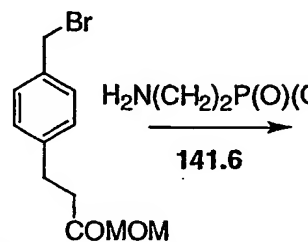


141.3

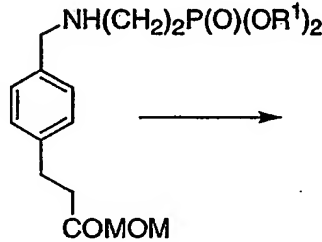
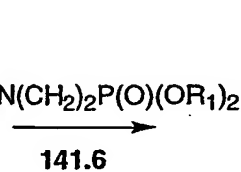


141.4

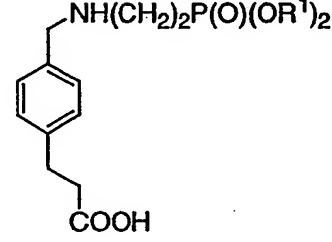
Example



141.5



141.7

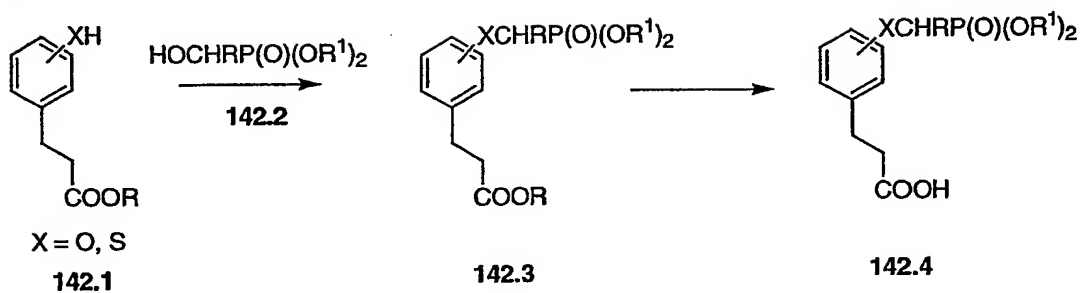


141.8

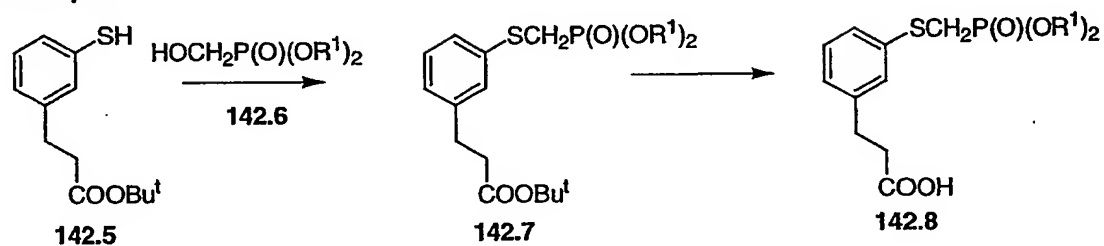
MOM = OCH₂OCH₃

Scheme 142

Method

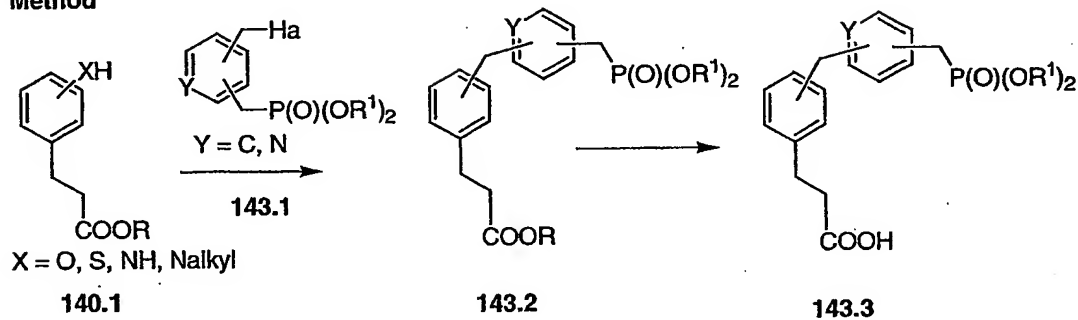


Example

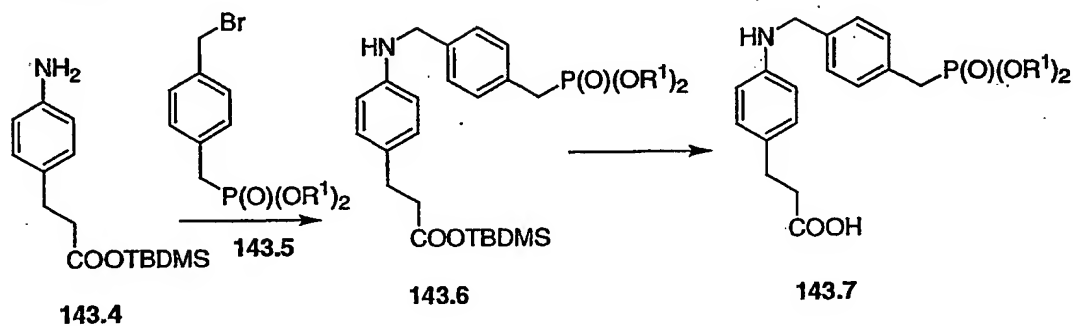


Scheme 143

Method



Example



Preparation of the phosphonate-containing thiophenol derivatives 7.1.

Schemes 144 - 153 describe the preparation of phosphonate-containing thiophenol derivatives 7.1 which are employed in the preparation of the phosphonate ester intermediates 2, 14 and 19 in which X is sulfur, and of the intermediate 15 in which X' is sulfur.

Scheme 144 depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol 144.1 is protected to afford the product 144.2. The protection and deprotection of thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277. For example, thiol substituents are protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a chlorotrialkylsilane and a base such as imidazole. Alternatively, thiol substituents are protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The product is then coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 144.3, to afford the phosphonate ester 144.4. The preparation of arylphosphonates by the coupling of aryl halides with dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The thiol protecting group is then removed, as described above, to afford the thiol 144.5.

For example, 3-bromothiophenol 144.6 is converted into the 9-fluorenylmethyl (Fm) derivative 144.7 by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite 144.3 to afford the phosphonate ester 144.8. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The compound 144.7 is reacted, in toluene solution at reflux, with a dialkyl phosphite 144.3, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 144.8. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol 144.9.

Using the above procedures, but employing, in place of 3-bromothiophenol 144.6, different thiophenols 144.1, and/or different dialkyl phosphites 144.3, the corresponding products 144.5 are obtained.

5 Scheme 145 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol 145.2 is metallated, for example by reaction with magnesium or by transmetallation with an alkylolithium reagent, to afford the metallated derivative 145.3. The latter compound is reacted with a halodialkyl phosphite 145.4 to afford the product 145.5; deprotection then affords the
10 thiophenol 145.6

For example, 4-bromothiophenol 145.7 is converted into the S-triphenylmethyl (trityl) derivative 145.8, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 287. The product is converted into the lithium derivative 145.9 by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio
15 compound is reacted with a dialkyl chlorophosphite 145.10 to afford the phosphonate 145.11. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol 145.12.

Using the above procedures, but employing, in place of the bromo compound 145.7, different halo compounds 145.1, and/or different halo dialkyl phosphites 145.4, there are obtained the
20 corresponding thiols 145.6.

Scheme 146 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol 146.1 is subjected to free-radical bromination to
25 afford a bromomethyl product 146.2. This compound is reacted with a sodium dialkyl phosphite 146.3 or a trialkyl phosphite, to give the displacement or rearrangement product 146.4, which upon deprotection affords the thiophenol 146.5.

For example, 2-methylthiophenol 146.5 is protected by conversion to the benzoyl derivative 146.7, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product 146.8. This material is reacted with a sodium dialkyl
30 phosphite 146.3, as described in J. Med. Chem., 35, 1371, 1992, to afford the product 146.9.

Alternatively, the bromomethyl compound **146.8** is converted into the phosphonate **146.9** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **146.8** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. $100^\circ C$ to produce the phosphonate **146.9**. Deprotection of the phosphonate **146.9**, for example by treatment with aqueous ammonia, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiol **146.10**.

Using the above procedures, but employing, in place of the bromomethyl compound **146.8**, different bromomethyl compounds **146.2**, there are obtained the corresponding thiols **146.5**.

- 10 Scheme **147** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **147.1** is reacted with a dialkyl hydroxyalkylphosphonate **147.2** under the conditions of the Mitsunobu reaction, for example as described in Org. React., 1992, 42, 335, to afford the coupled product **147.3**. Deprotection then yields the O- or S-
15 linked products **147.4**.

For example, 3-hydroxythiophenol, **147.5**, is converted into the monotrityl ether **147.6**, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **147.7** in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound **147.8**.

- 20 Removal of the trityl protecting group, as described above, then affords the thiophenol **147.9**. Using the above procedures, but employing, in place of the phenol **147.5**, different phenols or thiophenols **147.1**, there are obtained the corresponding thiols **147.4**.

- Scheme **148** illustrates the preparation of thiophenols **148.4** bearing a phosphonate group
25 linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **148.1** is reacted with an activated ester, for example the trifluoromethanesulfonate **148.2**, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product **148.3**. Deprotection then affords the thiol **148.4**.

- For example, 4-methylaminothiophenol **148.5** is reacted in dichloromethane solution with one
30 equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 298, to afford the S-acetyl product **148.6**. This material is then reacted with a dialkyl

trifluoromethanesulfonyloxymethyl phosphonate **148.7**, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product **148.8**. Preferably, equimolar amounts of the phosphonate **148.7** and the amine **148.6** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient
5 temperatures, to afford the phosphonate product **148.8**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiophenol **148.9**.

Using the above procedures, but employing, in place of the thioamine **148.5**, different phenols, thiophenols or amines **148.1**, and/or different phosphonates **148.2**, there are obtained the
10 corresponding products **148.4**.

Scheme **149** illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate **149.2**. In this procedure, a suitably protected
15 hydroxy, thio or amino substituted thiophenol **149.1** is reacted with a dialkyl bromoalkyl phosphonate **149.2** to afford the product **149.3**. Deprotection then affords the free thiophenol **149.4**.

For example, 3-hydroxythiophenol **149.5** is converted into the S-trityl compound **149.6**, as described above. This compound is then reacted with a dialkyl 4-bromobutyl phosphonate
20 **149.7**, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°C to yield the ether product **149.8**. Deprotection, as described above, then affords the thiol **149.9**.

25 Using the above procedures, but employing, in place of the phenol **149.5**, different phenols, thiophenols or amines **149.1**, and/or different phosphonates **149.2**, there are obtained the corresponding products **149.4**.

Scheme **150** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by
30 means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **150.2** is coupled with an aromatic bromo compound **150.1**. The coupling of aryl halides with olefins

- by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as
- 5 tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **150.3**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **150.4**, or the saturated analog **150.6**.
- 10 For example, 3-bromothiophenol is converted into the S-Fm derivative **150.7**, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate **150.8**, the preparation of which is described in *J. Med. Chem.*, 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in *J. Med. Chem.*, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar
- 15 solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **150.9**. Deprotection, as described above, then affords the thiol **150.10**. Optionally, the initially formed unsaturated phosphonate **150.9** is subjected to catalytic or chemical reduction, for example using diimide, as described in Scheme **138**, to yield the saturated product **150.11**, which upon deprotection affords the thiol **150.12**.
- 20 Using the above procedures, but employing, in place of the bromo compound **150.7**, different bromo compounds **150.1**, and/or different phosphonates **150.2**, there are obtained the corresponding products **150.4** and **150.6**

- Scheme **151** illustrates the preparation of an aryl-linked phosphonate ester **151.4** by means of
- 25 a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **151.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in *J. Org. Chem.*, 49, 5237, 1984. A coupling reaction then affords the
- 30 diaryl product **151.3** which is deprotected to yield the thiol **151.4**.
- For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in *Protective Groups in Organic*

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **151.5**. This material is reacted with a dialkyl 4-bromophenylphosphonate **151.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **151.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **151.8**. Using the above procedures, but employing, in place of the boronate **151.5**, different boronates **151.1**, and/or different phosphonates **151.2**, there are obtained the corresponding products **151.4**.

Scheme 152 depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **152.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **152.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **152.3** is then deprotected to afford the thiol **152.4**.

For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **152.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **152.5** is then reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, **152.6**, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C. The thioether product **152.7** thus obtained is deprotected, as described above, to afford the thiol **152.8**.

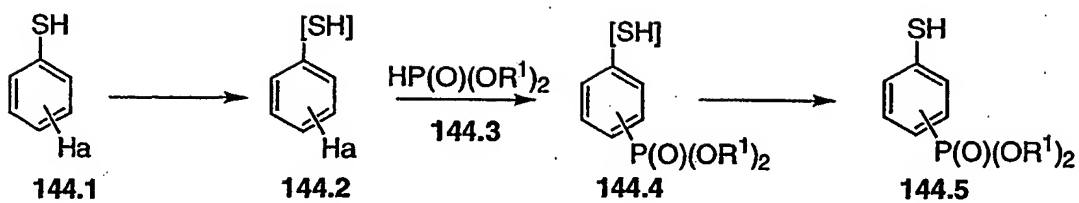
Using the above procedures, but employing, in place of the thiophenol **152.5**, different phenols, thiophenols or amines **152.1**, and/or different phosphonates **152.2**, there are obtained the corresponding products **152.4**.

Scheme 153 illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

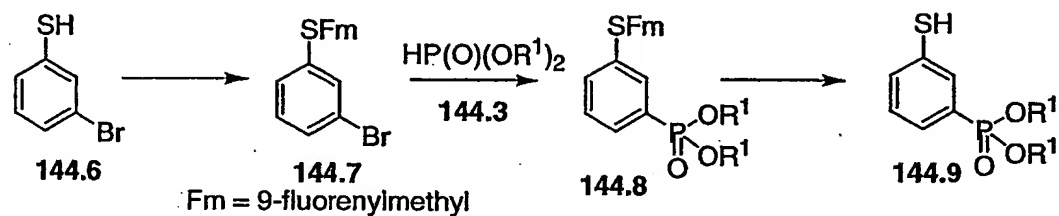
In this procedure, a suitably protected thiophenol **153.1**, for example an indoline (in which X-Y is $(\text{CH}_2)_2$), an indole (X-Y is $\text{CH}=\text{CH}$) or a tetrahydroquinoline (X-Y is $(\text{CH}_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **153.2**, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **153.3**. Deprotection, as described above, then affords the thiol **153.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines are also obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines are also obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p. 707. For example, 2,3-dihydro-1H-indole-5-thiol, **153.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **153.6**, as described above, and the ester is then reacted with the trifluoromethanesulfonate **153.7**, using the conditions described above for the preparation of the phosphonate **148.8**, (Scheme 148), to yield the phosphonate **153.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **153.9**. Using the above procedures, but employing, in place of the thiol **153.5**, different thiols **153.1**, and/or different triflates **153.2**, there are obtained the corresponding products **153.4**.

Scheme 144

Method

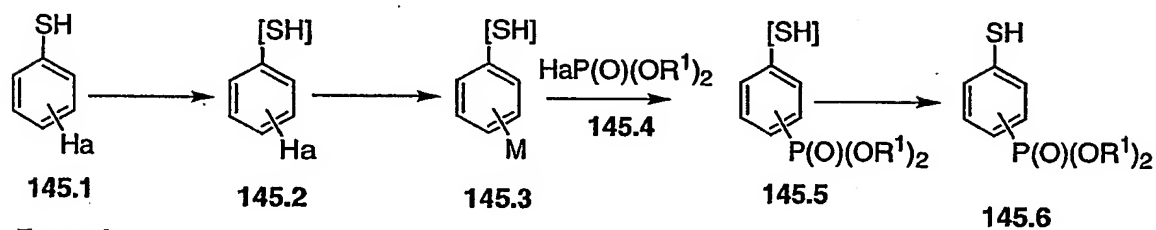


Example

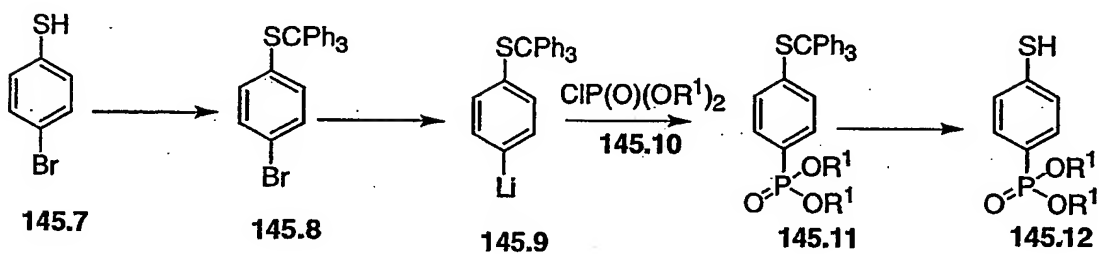


Scheme 145

Method

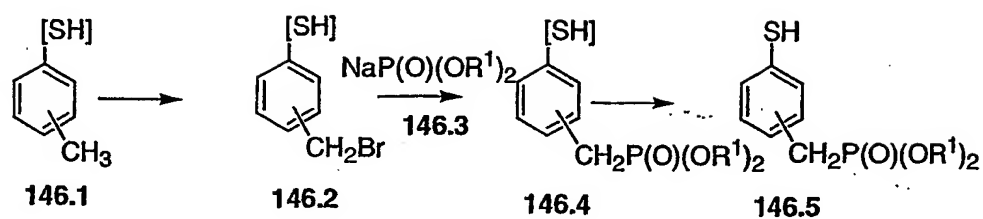


Example

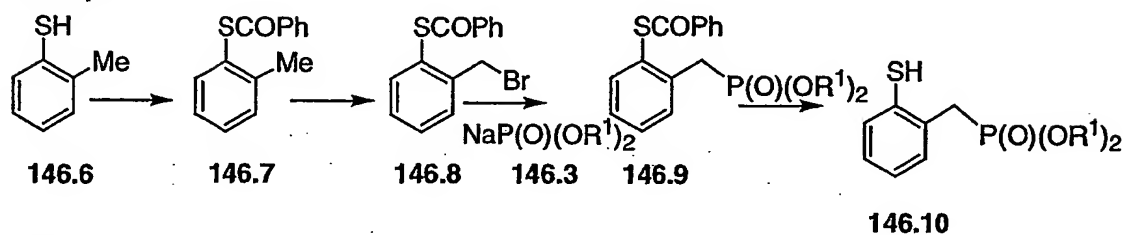


Scheme 146

Method

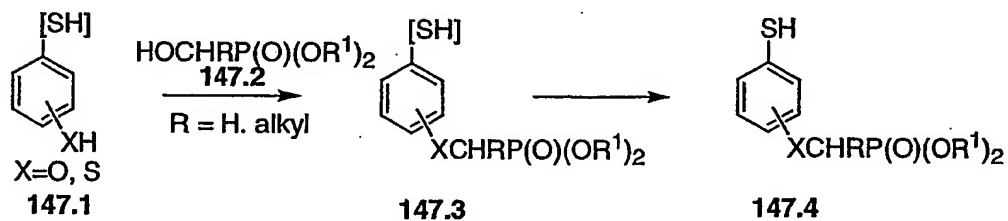


Example

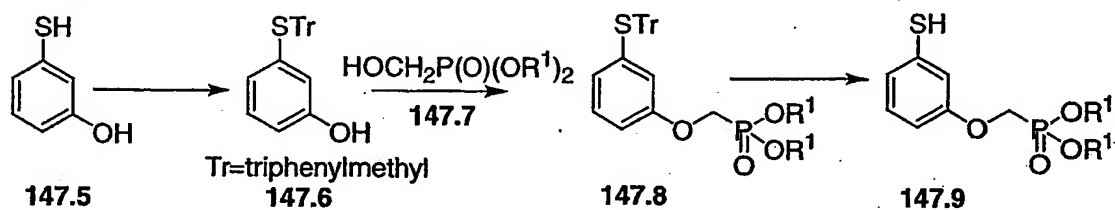


Scheme 147

Method

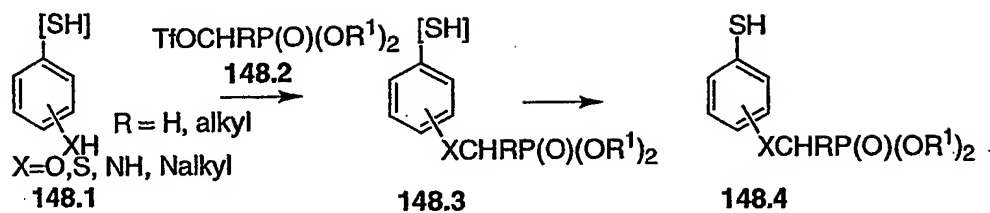


Example

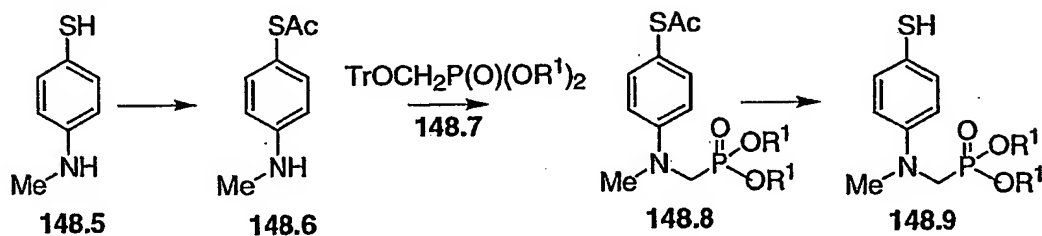


Scheme 148

Method

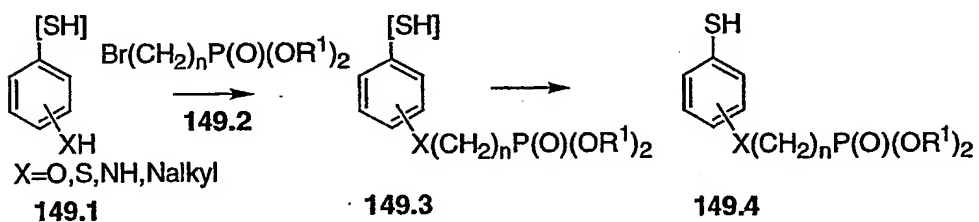


Example

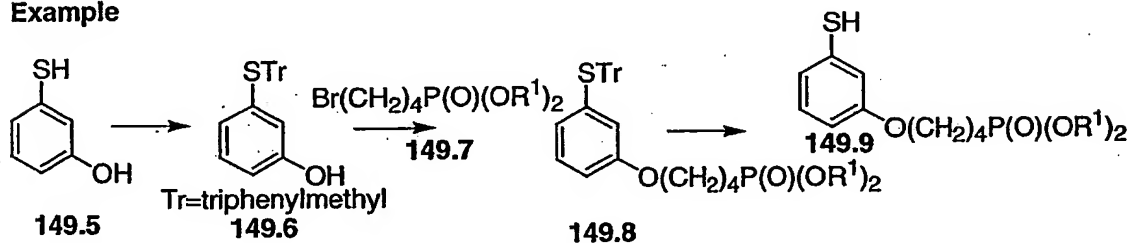


Scheme 149

Method

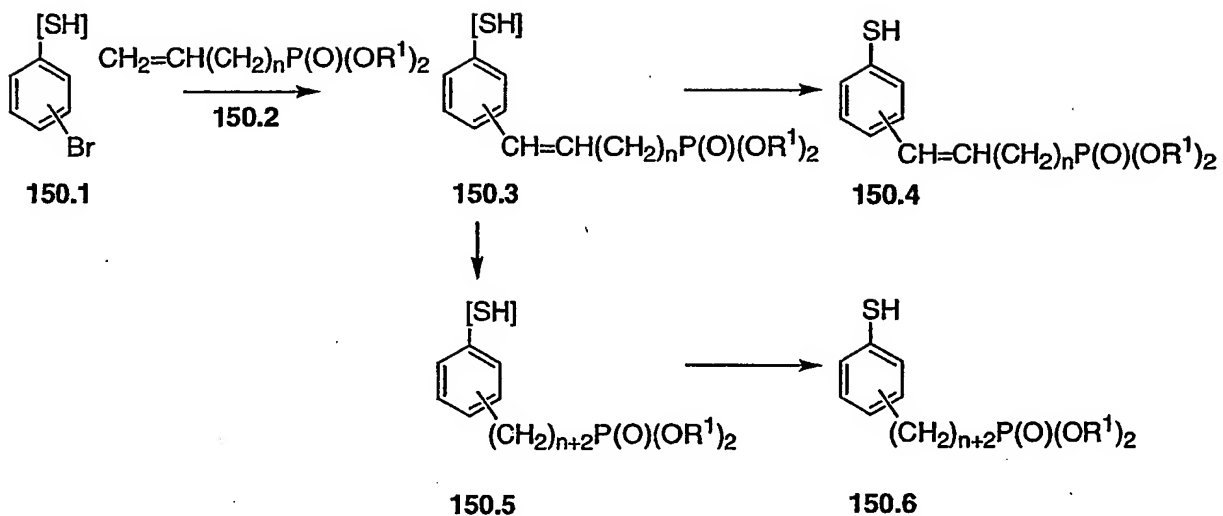


Example

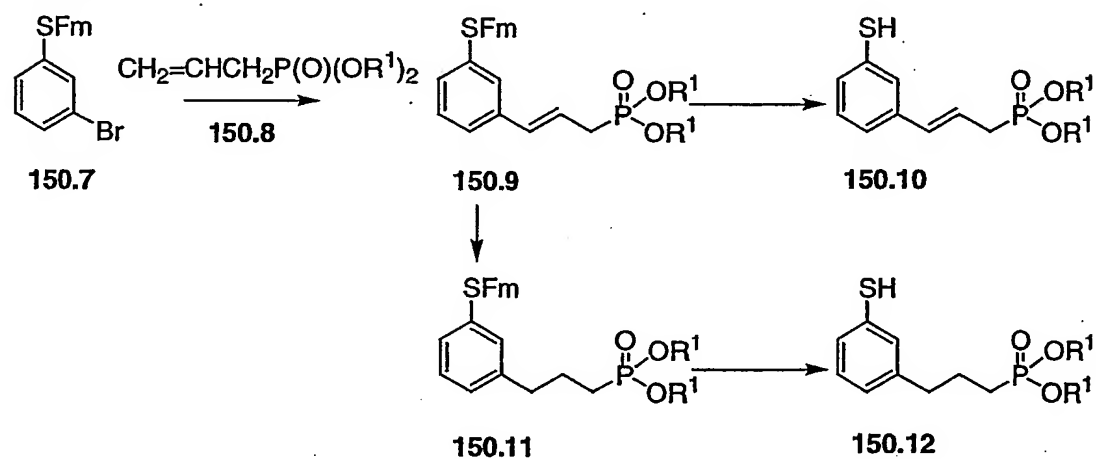


Scheme 150

Method

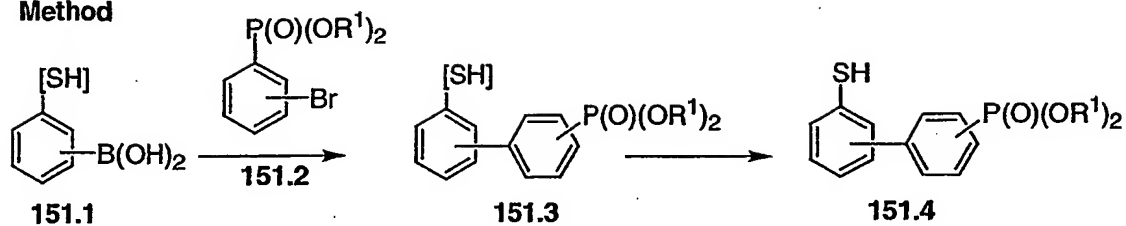


Example

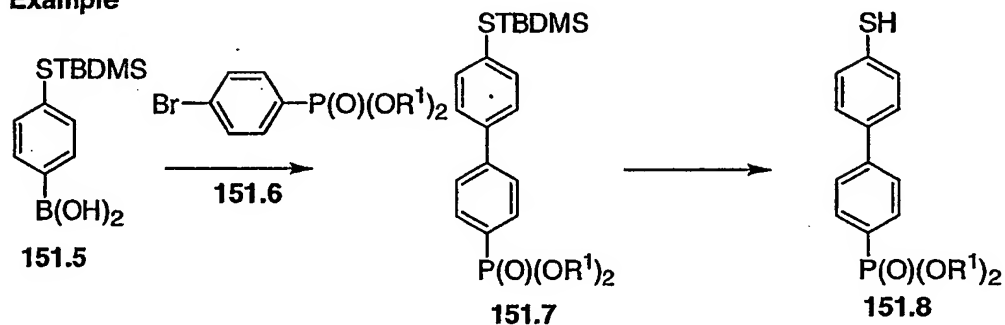


Scheme 151

Method

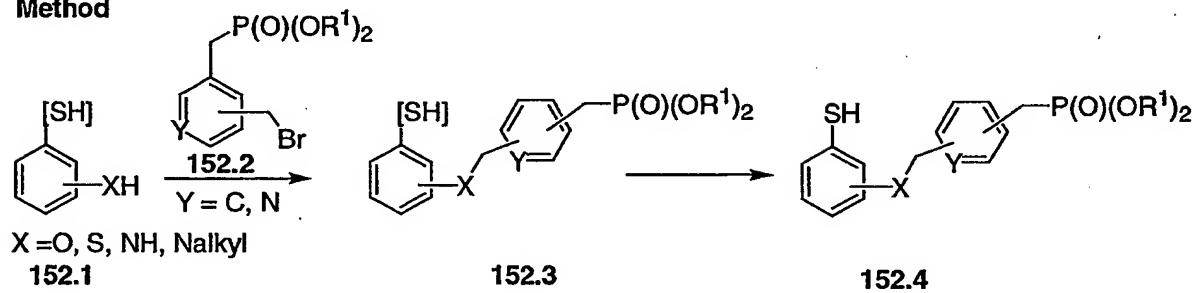


Example

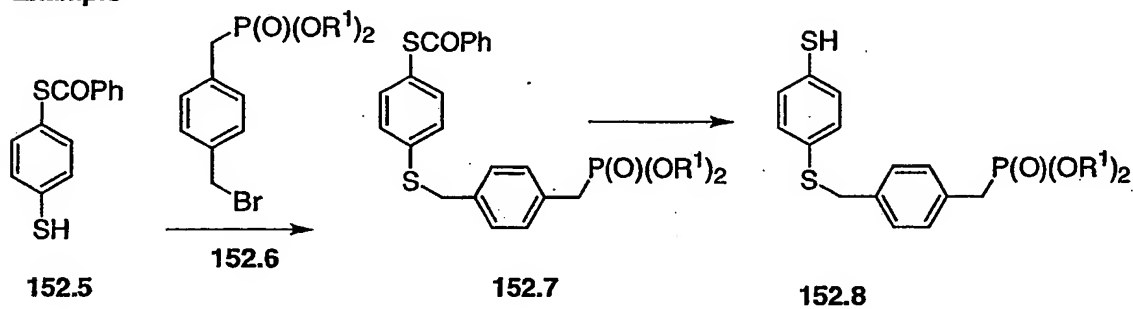


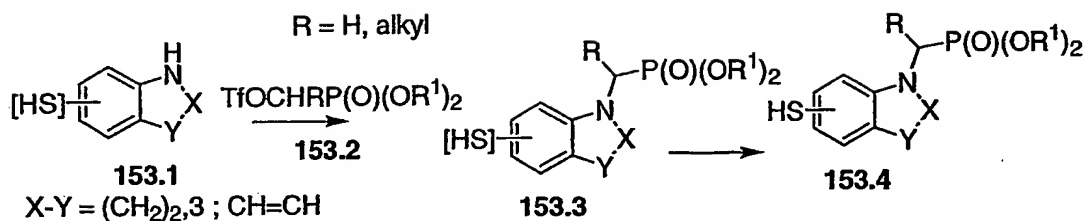
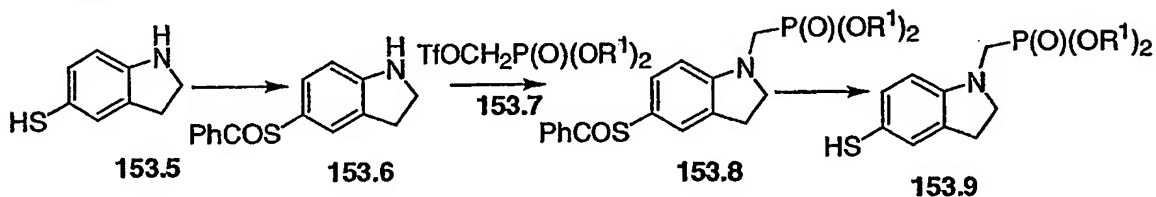
Scheme 152

Method



Example



Scheme 153**Method****Example**

Preparation of tert-butylamine derivatives 9.3 and 25.4 incorporating phosphonate groups.

5

Schemes 154 – 158 illustrate the preparation of the tert. butylamine derivatives 9.3 and 25.4 in which the substituent A is either the group link P(O)(OR¹)₂ or a precursor, such as [OH], [SH], Br, which are employed in the preparation of the intermediate phosphonate esters 3, 7, 11 and 20.

10

Scheme 154 describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2,2-dimethyl-2-aminoethyl bromide **154.1** is reacted with a trialkyl phosphite **154.2**, under the conditions of the Arbuzov reaction, as described in Scheme 137, to afford the phosphonate **154.3**, which is then deprotected to give the amine **154.4**.

15

For example, the cbz derivative of 2,2-dimethyl-2-aminoethyl bromide **154.6**, is heated with a trialkyl phosphite at ca 150°C to afford the product **154.7**. Deprotection then affords the free amine **154.8**. The removal of carbobenzyloxy substituents to afford the corresponding amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion is effected by the use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a palladium catalyst. Alternatively, the cbz group is removed by treatment of the substrate with triethylsilane,

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triethylamine and a catalytic amount of palladium (II) chloride, as described in Chem. Ber., 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient temperature, as described in J. Chem. Soc., Perkin Trans. I, 1277, 1988. The cbz group is also removed by treatment with Lewis acid such as boron tribromide, as described in J. Org. Chem., 39, 1247, 5 1974, or aluminum chloride, as described in Tet. Lett., 2793, 1979.

Using the above procedures, but employing different trialkyl phosphites, there are obtained the corresponding amines 154.4.

Scheme 155 illustrates the preparation of phosphonate esters attached to the tert butylamine 10 by means of a heteroatom and a carbon chain. A protected alcohol or thiol 155.1 is reacted with a dialkyl bromoalkylphosphonate 155.2, to afford the displacement product 155.3. Deprotection, if needed, then yields the amine 155.4.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol 155.5 is reacted with a dialkyl 4-bromobutyl phosphonate 155.6, prepared as described in Synthesis, 1994, 9, 909, in 15 dimethylformamide containing potassium carbonate and a catalytic amount of potassium iodide, at ca 60° to afford the phosphonate 155.7. Deprotection, by hydrogenation over a palladium catalyst, then affords the free amine 155.8.

Using the above procedures, but employing different alcohols or thiols 155.1, and/or different bromoalkylphosphonates 155.2, there are obtained the corresponding ether and thioether 20 products 155.4.

Scheme 156 describes the preparation of carbon-linked tert. butylamine phosphonate derivatives, in which the carbon chain is unsaturated or saturated.

In the procedure, a terminal acetylenic derivative of tert-butylamine 156.1 is reacted, under 25 basic conditions, with a dialkyl chlorophosphite 156.2, to afford the acetylenic phosphonate 156.3. The coupled product 156.3 is deprotected to afford the amine 156.4. Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products 156.5 and 156.6 respectively.

For example, 2-amino-2-methylprop-1-yne 156.7, the preparation of which is described in WO 30 9320804, is converted into the N-phthalimido derivative 156.8, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide

in tetrahydrofuran at -78°C. The resultant anion is then reacted with a dialkyl chlorophosphite 156.2 to afford the phosphonate 156.9. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine 156.10. Partial catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents
5 for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p. 566, produces the olefinic phosphonate 156.11, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate 156.12. Using the above procedures, but employing different acetylenic amines 156.1, and/or different
10 dialkyl halophosphites, there are obtained the corresponding products 156.4, 156.5 and 156.6.

Scheme 157 illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

In this method, an aminopropyl-substituted cyclic amine 157.1 is reacted with a limited
15 amount of a bromoalkyl phosphonate 157.2, using, for example, the conditions described above (Scheme 149) to afford the displacement product 157.3.

For example, 3-(1-amino-1-methyl)ethylpyrrolidine 157.4, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with one molar equivalent of a dialkyl 4-bromobutyl phosphonate 157.5, prepared as described in Synthesis, 1994, 9, 909, to
20 afford the displacement product 157.6.

Using the above procedures, but employing, in place of 3-(1-amino-1-methyl)ethylpyrrolidine 157.4, different cyclic amines 157.1, and/or different bromoalkylphosphonates 157.2, there are obtained the corresponding products 157.3.

25 Scheme 158 illustrates the preparation of the amides 9.3 which are employed in the preparation of the phosphonate esters 3. In this procedure, the carboxylic acids 158.1, the structures of which are illustrated in Chart 10, compounds C1 - C16, are converted into the BOC-protected derivatives 155.8. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and
30 P.G.M Wuts, Wiley, Second Edition 1990, p. 327. For example, the amine is reacted with di-tert-butoxycarbonylanhydride (BOC anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), and the like. The carboxylic acid

158.2 is then coupled, as described in Scheme 1, with the tert. butylamine derivatives 25.4, or precursors thereto, the preparation of which is described in Schemes 154 - 157, to afford the amide 158.3. The BOC group is then removed to yield the amine 9.3. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection is effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preparation of pyridine intermediates 13.1 incorporating phosphonate substituents.

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Schemes 159 - 163, described the preparation of chloromethyl or formyl pyridine derivatives incorporating phosphonate moieties. Scheme 164 illustrates the conversion of the above compounds into the piperazine derivatives 13.1 which are employed in the preparation of the phosphonate esters 4.

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Scheme 159 illustrates the preparation of chloromethyl-substituted pyridines in which a phosphonate moiety is directly attached to the pyridine ring.

In this procedure, a halo-substituted methylpyridine 159.1 is reacted with a dialkyl phosphite 159.2, to afford the phosphonate product 159.3. The coupling reaction is conducted in the presence of a palladium (0) catalyst, for example as described in J. Med. Chem., 35, 1371, 1992. The product 159.3 is then converted into the chloromethyl derivative 159.4 by means of a chlorination reaction. The chlorination of benzylic methyl groups is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 313. A variety of free-radical chlorinating agents are employed.

For example, 3-bromo-5-methylpyridine, 159.5 (ChemPacific) is reacted with an equimolar amount of a dialkyl sodium phosphite, 13.2 in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, in toluene at reflux, to yield the phosphonate 159.6. The latter compound is then chlorinated, for example by the use of one molar equivalent of phenyliodonium dichloride, as described in J. Org. Chem., 29, 3692, 1964, to prepare the chloromethyl compound 159.7.

Using the above procedures, but employing, in place of the bromomethyl pyridine 159.5, different halomethyl pyridines 159.1, and/or different dialkyl phosphites 159.2 the corresponding products 159.4 are obtained.

Scheme 160 depicts the preparation of chloromethyl pyridines incorporating a phosphonate group attached to the pyridine ring by means of a carbon link. In this procedure, a bis(chloromethyl)pyridine 160.1 is reacted with a sodium dialkyl phosphite 146.3, employing, for example, procedures described in J. Med. Chem., 35, 1371, 1992, to afford the displacement product 160.2.

For example, 3,5-bis(chloromethyl)pyridine 160.3, the preparation of which is described in Eur. J. Inorg. Chem., 1998, 2, 163, is reacted with one molar equivalent of a dialkyl sodium phosphite 146.3 in tetrahydrofuran, at ambient temperature, to afford the product 160.4.

Using the above procedures, but employing, in place of the bis(chloromethyl) compound 160.3, different bis(chloromethyl) pyridines 160.1, and/or different dialkyl sodium phosphites 146.3 the corresponding products 160.2 are obtained.

Scheme 161 illustrates the preparation of pyridine aldehydes incorporating a phosphonate group linked to the pyridine nucleus by means of a saturated or unsaturated carbon chain. In this procedure, a suitably protected halo-substituted pyridine carboxaldehyde 161.1 is coupled, by means of a palladium-catalyzed Heck reaction, as described in Scheme 150, with a dialkyl alkenyl phosphonate 161.2. Methods for the protection of aldehydes are described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 175. The protected aldehyde 161.1 is reacted with an olefinic phosphonate 161.2, in the presence of a palladium (0) catalyst, to afford the coupled product 161.3. Deprotection of the aldehyde group then affords the product 161.6. Alternatively, the unsaturated compound 161.3 is reduced to afford the saturated analog 161.5, which upon deprotection yields the saturated analog 161.7. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, and chemical reduction, the latter for example employing diborane or diimide.

For example, 5-bromopyridine-3-carboxaldehyde 161.8 (ChemPacific) is converted into the dimethyl acetal, by reaction with methanolic ammonium chloride, as described in J. Org. Chem., 26, 1156, 1961. The acetal 161.9 is then reacted with a dialkyl butenyl phosphonate 161.10, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of bis(triphenylphosphine) palladium(II) chloride, as described in J. Med. Chem., 1992, 35, 1371, to afford the coupled product 161.11. Deprotection, for example by treatment with formic acid in pentane, as described in Synthesis, 651, 1983, yields the free aldehyde 161.13.

The product is reduced, for example by reaction with diimide, as described in J. Org. Chem., 30, 3965, 1965, to afford the saturated product **161.12**.

Using the above procedures, but employing, in place of the aldehyde **161.8**, different aldehydes **161.1**, and/or different phosphonates **161.2**, the corresponding products **161.6** and
5 **161.7** are obtained.

Scheme **162** illustrates the preparation of pyridine aldehydes incorporating a phosphonate group linked to the pyridine by a heteroatom and a carbon chain. In this procedure, a 2- or 4-halo-substituted pyridine aldehyde **162.1** is reacted with a dialkyl hydroxy- or thio-alkylphosphonate **162.2**. The preparation of alkoxy- or thioalkoxy-pyridines by the reaction of alkoxy- or thioalkoxy-pyridines with alcohols or thiols is described, for example, in J. Am. Chem. Soc., 82, 4414, 1960. The
10 preparation of pyridine thioethers by reaction of halopyridines with thiols is described, for example, in Chemistry of Heterocyclic Compounds, Pyridine and its derivatives, E. Klingsberg, Ed, part 4, p. 358. The alcohols and thiols are transformed into metal salts, for example sodium or potassium salts, and then reacted with the halopyridine substrates at
15 elevated temperatures, optionally in the presence of copper powder catalyst, to afford the ether or thioether products **162.3**.

For example, a tetrahydrofuran solution of 2-bromo-pyridine-5-aldehyde **162.4**, prepared as described in Tet. Lett., 2001, 42, 4841, is heated at reflux with an equimolar amount of a dialkyl 2-mercaptoethylphosphonate **162.5**, the preparation of which is described in Aust. J.
20 Chem., 43, 1123, 1990, in the presence of sodium carbonate, to afford the thioether product **162.6**.

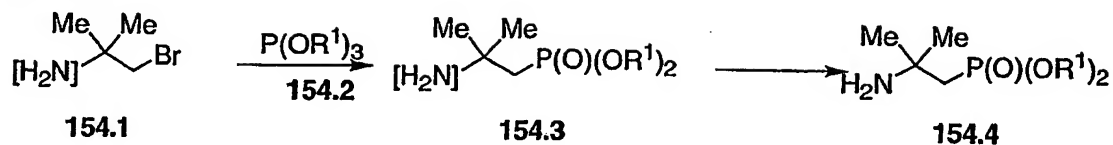
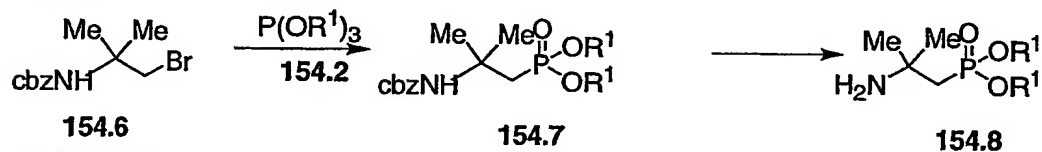
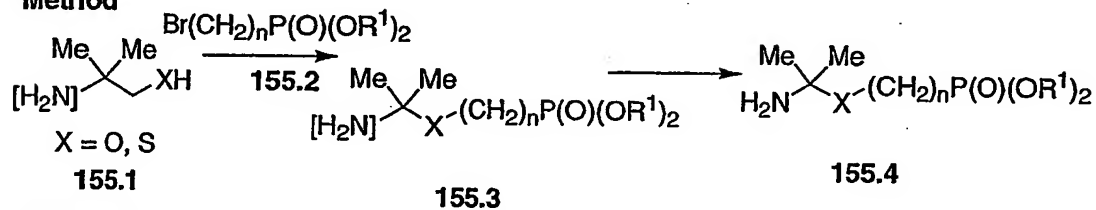
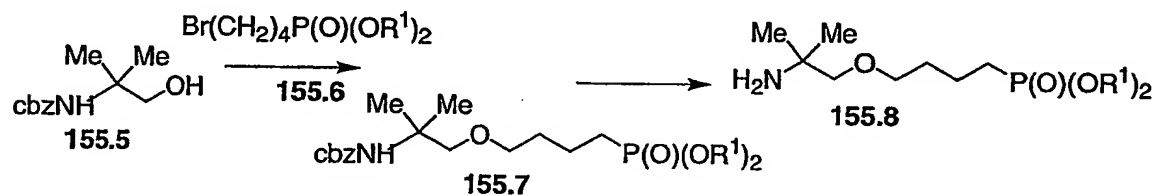
Using the above procedures, but employing, in place of the haloaldehyde **162.4**, different haloaldehydes **162.1**, and/or different hydroxy or thio-alkyl phosphonates **162.2**, the corresponding products **162.3** are obtained.

25 Scheme **163** depicts the preparation of pyridine aldehydes **163.3** in which the phosphonate group is attached to the pyridine nucleus by means of a chain incorporating a nitrogen atom. In this procedure, a pyridine dicarboxaldehyde **163.1** is reacted with a dialkyl aminoalkyl phosphonate **163.2**, in the presence of a reducing agent, so as to effect a reductive amination reaction, yielding the product **163.3**. The preparation of amines by means of reductive
30 amination of aldehydes is described, for example, in Advanced Organic Chemistry, F. A.

Carey, R. J. Sundberg, Plenum, 2001, part B, p. 269. The reactants are combined in an inert solvent such as an alcohol or ether, and treated with a reducing agent such as, for example, sodium cyanoborohydride or sodium triacetoxy borohydride, so as to yield the amine product 163.3.

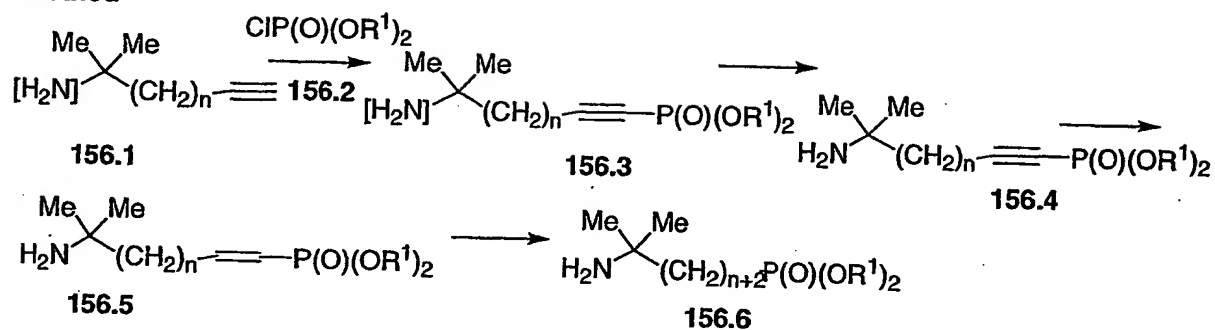
- 5 For example, equimolar amounts of pyridine 3,5-dicarboxaldehyde 163.4, prepared as described in Tet. Lett., 1994, 35, 6191, and a dialkyl 2-aminoethyl phosphonate 163.5 prepared as described in J. Org. Chem., 2000, 65, 676, are reacted with sodium cyanoborohydride in isopropanol containing acetic acid, at ambient temperature, so as to produce the amine product 163.6
- 10 Using the above procedures, but employing, in place of the dicarboxaldehyde 163.4, different dicarboxaldehydes 163.1, and/or different aminoalkyl phosphonates 163.2, the corresponding products 163.3 are obtained.

- Scheme 164 illustrates the incorporation of the formyl or chloromethyl pyridines, the syntheses of which are described above, into the piperazine reagent 13.1. Compounds 164.2 in which Z is chloromethyl are reacted with the mono-protected piperazine derivatives 164.1, the preparation of which are described in WO 9711698, to afford the alkylated product 164.3. The preparation of amines by means of alkylation reactions is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 397. Equimolar amounts of the reactants 164.1 and the halomethyl pyridine compound 164.2, are combined in a organic solvent such as an alcohol or dimethylformamide, in the presence of a base such as triethylamine or potassium carbonate, to give the alkylated products 164.3. The alkylation of a piperazine derivative by a 3-chloromethylpyridine is described in WO9628439. Alternatively, the amine 164.1 is reacted with the aldehyde 164.2 to afford the product 164.3 in a reductive alkylation reaction. The preparation of amines by means of reductive amination procedures is described in Scheme 163. In this procedure, the amine component and the aldehyde component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The reductive alkylation reaction between 3-pyridinecarboxaldehyde and a substituted piperazine is described in WO9628439. Deprotection of the product 164.3 then yields the free amine 13.1.

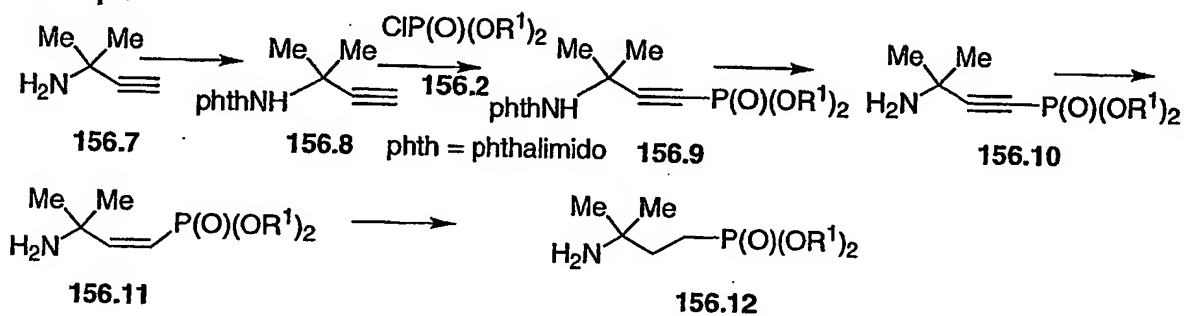
Scheme 154**Method****Example****Scheme 155****Method****Example**

Scheme156

Method

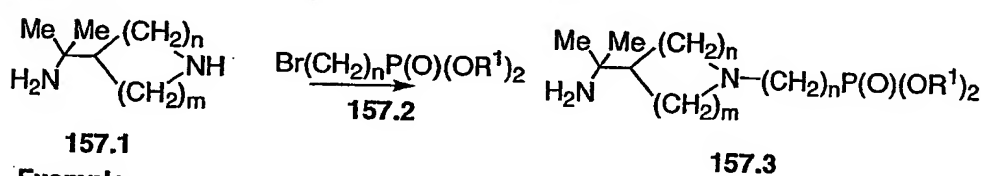


Example

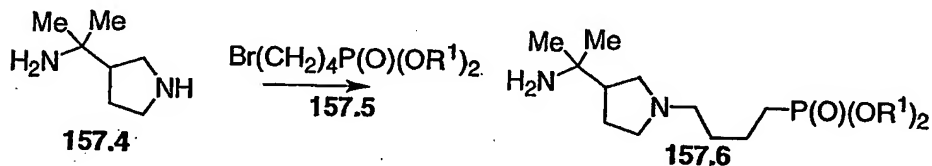


Scheme 157

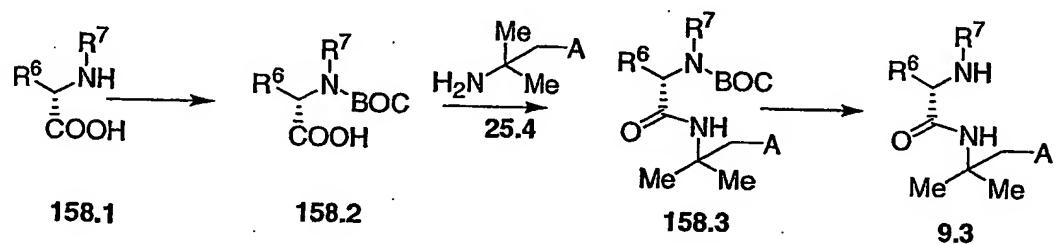
Method



Example

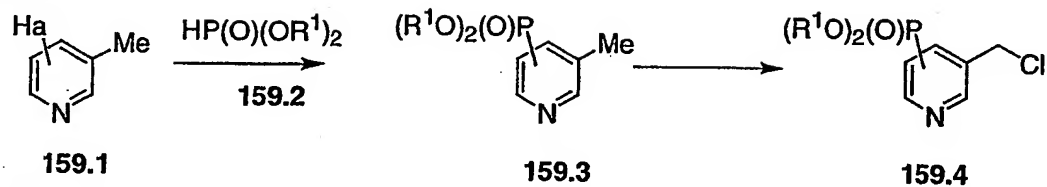


Scheme 158

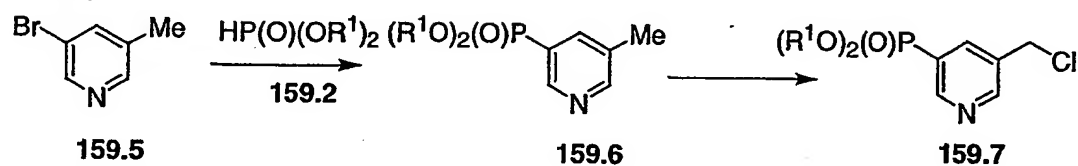


Scheme 159

Method

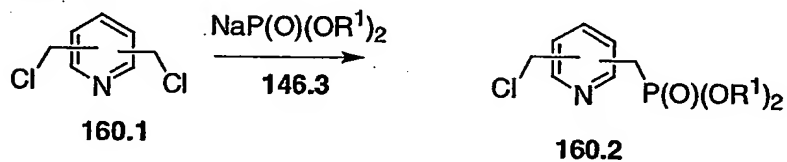


Example

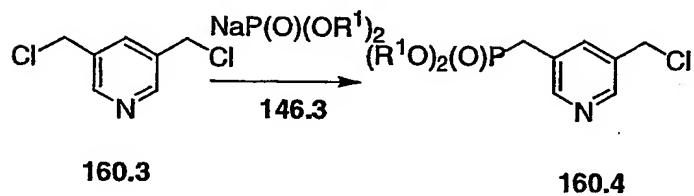


Scheme 160

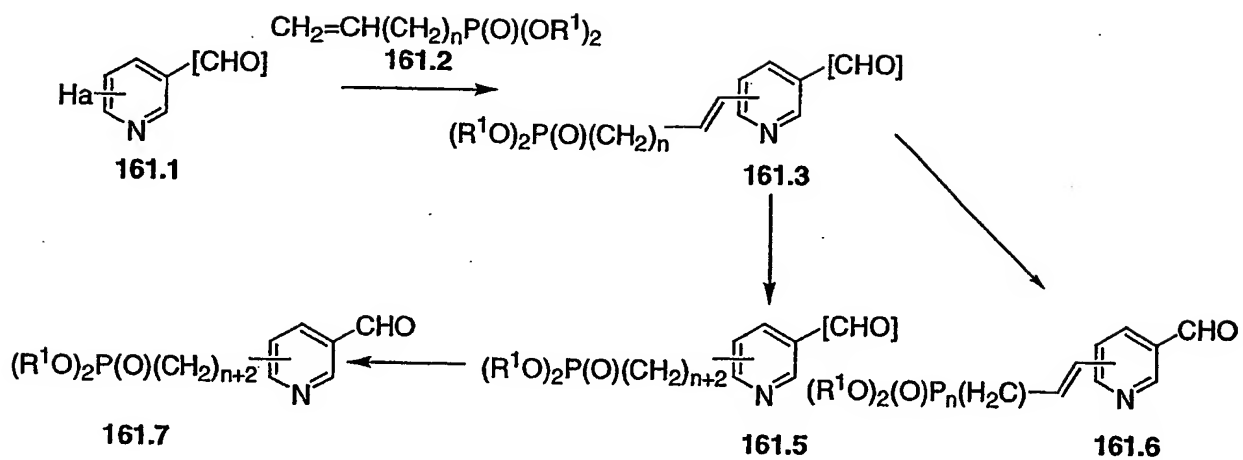
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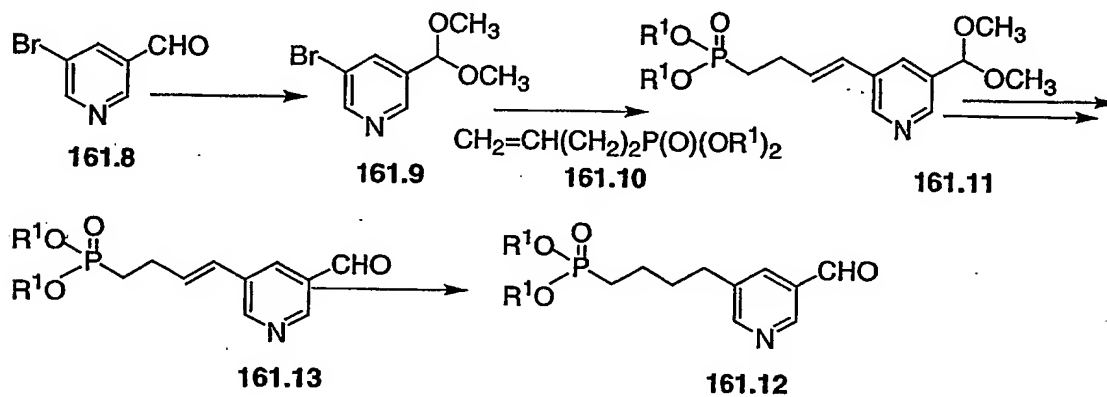
Example

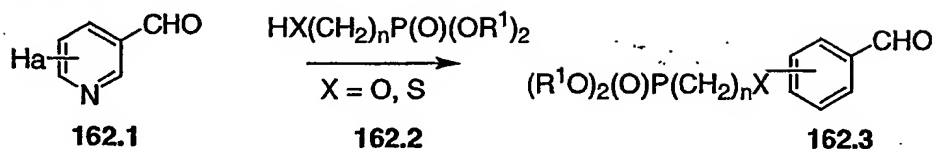
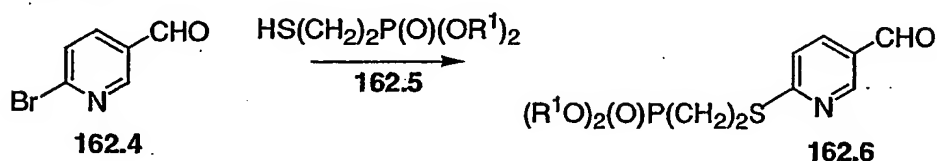
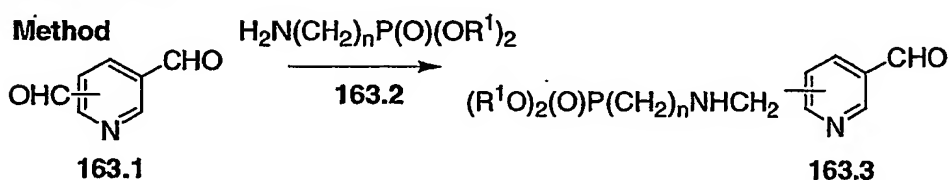
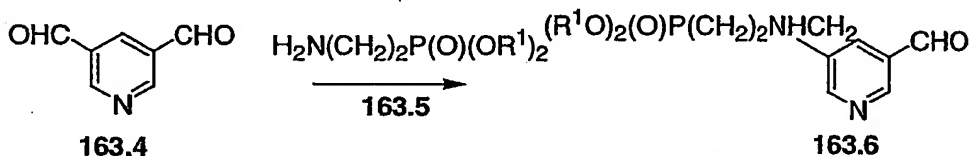
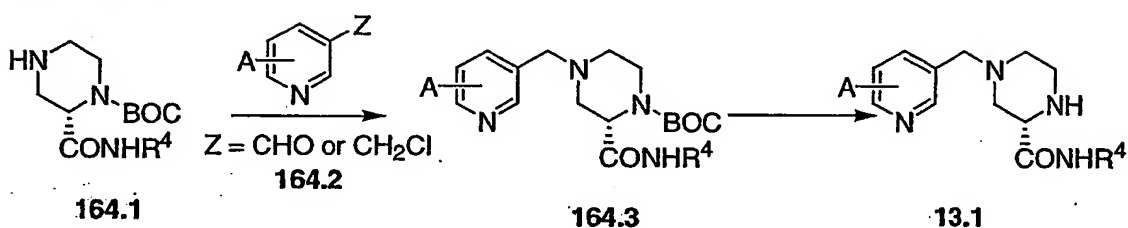


Scheme 161
Method



Example



Scheme 162**Method****Example****Scheme 163****Method****Example****Scheme 164****Preparation of dimethoxybenzyl halides 49.7 incorporating phosphonate groups.**

- 5 Schemes 165 - 169 illustrate the preparation of dimethoxybenzyl halides 49.7 incorporating phosphonate groups, which are employed in the synthesis of the phosphonate esters 6 and 13.

Scheme 165 depicts the preparation of dimethoxybenzyl alcohols in which the phosphonate group is attached either directly to the phenyl ring or by a saturated or unsaturated alkylene

chain. In this procedure, a bromo-substituted dimethoxy benzyl alcohol is coupled, in the presence of a palladium catalyst, with a dialkyl alkenyl phosphonate **165.2**, to afford the coupled product **165.3**. The reaction is conducted under the conditions described in Scheme **150**. The product **165.3** is then reduced, for example by treatment with diimide, as described in Scheme **150**, to yield the saturated analog **165.4**. Alternatively, the bromo compound **165.1** is coupled, in the presence of a palladium catalyst, as described in Scheme **144**, with a dialkyl phosphite **165.5**, to afford the phosphonate **165.6**.

For example, 4-bromo-3,5-dimethoxybenzyl alcohol **165.7**, the preparation of which is described in J. Med. Chem., 1977, 20, 299, is coupled with a dialkyl allyl phosphonate **165.8** (Aldrich) in the presence of bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **165.9**. The product is reduced, for example by treatment with diimide, as described in J. Org. Chem., 52, 4665, 1987, to yield the saturated compound **165.10**.

Using the above procedures, but employing, in place of the dimethoxy bromobenzyl alcohol **165.7**, different benzyl alcohols **165.1**, and/or different alkenyl phosphonates **165.2**, the corresponding products **165.3** and **165.4** are obtained.

As a further example, 3-bromo-4,5-dimethoxybenzyl alcohol **165.11**, the preparation of which is described in J. Org. Chem., 1978, 43, 1580, is coupled, in toluene solution at reflux, with a dialkyl phosphite **165.5**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to yield the phenyl phosphonate **165.12**.

Using the above procedures, but employing, in place of the dimethoxy bromobenzyl alcohol **165.11**, different benzyl alcohols **165.1**, and/or different dialkyl phosphites **165.5**, the corresponding products **165.6** are obtained.

Scheme **166** illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an amide group. In this procedure, a carboxy-substituted dimethoxybenzyl alcohol **166.1** is coupled, as described in Scheme **1**, with a dialkyl aminoalkyl phosphonate **166.2** to prepare the amide **166.3**.

For example, 2,6-dimethoxy-4-(hydroxymethyl)benzoic acid **166.4**, the preparation of which is described in Chem. Pharm. Bull., 1990, 38, 2118, is coupled in dimethylformamide solution, in

the presence of dicyclohexylcarbodiimide, with a dialkyl aminoethyl phosphonate 166.5, the preparation of which is described in J. Org. Chem., 2000, 65, 676, to afford the amide 166.6. Using the above procedures, but employing, in place of the dimethoxybenzoic acid 166.4, different benzoic acids 166.1, and/or different aminoalkyl phosphites 166.2, the corresponding products 166.3 are obtained.

Scheme 167 illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an aminoalkyl or an amide group. In this procedure, an amino-substituted dimethoxybenzyl alcohol 167.1 is reacted, under reductive amination conditions, as described in Scheme 163, with a dialkyl formylalkylphosphonate 167.2 to yield the aminoalkyl product 167.3. Alternatively, the amino-substituted dimethoxybenzyl alcohol 167.1 is coupled, as described in Scheme 1, with a dialkyl carboxyalkyl phosphonate 167.4, to produce the amide 167.5.

For example, 3-amino-4,5-dimethoxybenzyl alcohol 167.6, the preparation of which is described in Bull. Chem. Soc. Jpn., 1972, 45, 3455, is reacted, in the presence of sodium triacetoxymethylborohydride, with a dialkyl formylmethyl phosphonate 167.7, as described in Scheme 135, to afford the aminoethyl phosphonate 167.8.

Using the above procedures, but employing, in place of the amine 167.6, different amines 167.1, and/or different formylalkyl phosphites 167.2, the corresponding products 167.3 are obtained.

As a further example, 4-amino-3,5-dimethoxybenzyl alcohol 167.9, the preparation of which is described in Bull. Chem. Soc. Jpn., 1972, 45, 3455, is coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl phosphonoacetic acid 167.10, (Aldrich) to afford the amide 167.11.

Using the above procedures, but employing, in place of the amine 167.6, different amines 167.1, and/or different carboxyalkyl phosphonates 167.4, the corresponding products 167.5 are obtained.

Scheme 168 illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an alkoxy group. In this procedure, a dimethoxyhydroxy benzyl alcohol 168.1 is reacted with a dialkyl alkylphosphonate 168.2 with a terminal leaving group to afford the alkoxy product 168.3. The alkylation reaction is

effected in a polar organic solvent such as dimethylformamide in the presence of a base such as dimethylaminopyridine or cesium carbonate.

For example, 4-hydroxy-3,5-dimethoxybenzyl alcohol 168.4, the preparation of which is described in J. Med. Chem. 1999, 43, 3657, is reacted in dimethylformamide at 80°C with an equimolar amount of a dialkyl bromopropyl phosphonate 168.5, prepared as described in J. Am. Chem. Soc., 2000, 122, 1554, and cesium carbonate, to give the alkylated product 168.6. Using the above procedures, but employing, in place of the phenol 168.4, different phenols 168.1, and/or different alkyl phosphonates 168.2, the corresponding products 168.3 are obtained.

As a further example, 4,5-dimethoxy-3-hydroxybenzyl alcohol 168.7, prepared as described in J. Org. Chem., 1989, 54, 4105, is reacted, as described above, with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate 168.8, prepared as described in Tet. Lett., 1986, 27, 1477, to produce the alkylated product 168.9.

Using the above procedures, but employing, in place of the phenol 168.7, different phenols 168.1, and/or different alkyl phosphonates 168.2, the corresponding products 168.3 are obtained.

Scheme 169 illustrates the conversion of the benzyl alcohols 169.1, in which the substituent A is the group link-P(O)(OR¹)₂, or a precursor, prepared as described above, into the

corresponding halides 169.2. The conversion of alcohols into chlorides, bromides and iodides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff, p. 356ff and p. 358ff. For example, benzyl alcohols are transformed into the chloro compounds, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols are transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. Benzyl alcohols are transformed into iodides by reaction with sodium iodide and boron trifluoride etherate, as described in Tet. Lett., 28, 4969, 1987, or by reaction with diphosphorus tetraiodide, as described in Tet. Lett., 1801, 1979. Benzylic chlorides or bromides are transformed into the corresponding iodides by reaction with sodium iodide in acetone or methanol, for example as described in EP 708085.

Preparation of dimethoxythiophenols 23.1 incorporating phosphonate groups.

Schemes 170 - 173 illustrate the preparation of the dimethoxythiophenols 23.1 incorporating phosphonate groups, which are used in the synthesis of the phosphonate esters 6 and 13.

5

Scheme 170 illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached by means of an amide group. In this procedure, a dimethoxyamino-substituted benzoic acid 170.1 is converted into the corresponding thiol 170.2. The conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoroborate, is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to afford the thiol 170.2. The product is then coupled, as described above, with a dialkyl aminoalkyl phosphonate 170.3, to yield the amide 170.4.

10 For example, 5-amino-2,3-dimethoxybenzoic acid 170.5, the preparation of which is described in JP 02028185, is converted, as described above, into 2,3-dimethoxy-5-mercaptobenzoic acid 170.6. The product is then coupled, as described in Scheme 1, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminopropyl phosphonate 170.7, (Acros) to afford the amide 170.8.

20 Using the above procedures, but employing, in place of the amine 170.5, different amines 170.1, and/or different aminoalkyl phosphonates 170.3, the corresponding products 170.4 are obtained.

Scheme 171 illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromodimethoxyaniline 171.1 is converted, as described in Scheme 170, into the corresponding thiophenol 171.2. The thiol group is then protected to give the derivative 171.3. The protection and deprotection of thiol groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277.

30 For example, thiol substituents are protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a chlorotrialkylsilane and a base such as imidazole. Alternatively, thiol substituents are protected by conversion to tert-butyl or

adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The product 171.3 is then coupled, in the presence of a palladium catalyst, as described in Scheme 165, with a dialkyl alkenyl phosphonate 171.4, to give the alkenyl product 171.5. Deprotection then yields the thiol 171.6. Reduction of the double bond, for example by reaction with diimide, as described in J. Org. Chem., 52, 4665, 1987, affords the saturated product 171.7.

For example, 4-bromo-3,5-dimethoxyaniline 171.8, prepared as described in WO9936393, is converted, by diazotization, into 4-bromo-3,5-dimethoxythiophenol 171.9. The product is then transformed into the S-benzoyl derivative 171.10, by reaction with benzoyl chloride in pyridine, and the product is coupled, as described in Scheme 165, with a dialkyl butenyl phosphonate 171.11, the preparation of which is described in J. Med. Chem., 1996, 39, 949, to yield the phosphonate 171.12. Deprotection, for example by treatment with aqueous ammonia at ambient temperature, as described in J. Am. Chem. Soc., 85, 1337, 1963, then afford the thiol 171.13. The double bond is reduced with diimide to give the saturated analog 171.14.

Using the above procedures, but employing, in place of the amine 171.8, different amines 171.1, and/or different alkenyl phosphonates 171.4, the corresponding products 171.6 and 171.7 are obtained.

Scheme 172 illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group directly attached to the phenyl ring. In this procedure, a protected bromodimethoxythiophenol 172.1, prepared, for example, from the corresponding aniline, as described above, is coupled, in the presence of a palladium catalyst, as described in Scheme 165, with a dialkyl phosphite 172.2. The product is then deprotected to afford the phosphonate ester 172.4.

For example, 3-bromo-4,5-dimethoxyaniline 172.5, prepared as described in DE 2355394, is converted, as described above in Schemes 165 and 171, into S-benzoyl 3-bromo-4,5-dimethoxythiophenol 172.6. This compound is then coupled, in toluene solution at reflux, with a dialkyl phosphite 172.2, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to yield the phenyl phosphonate 172.7.

Deprotection, as described in Scheme 171, then affords the thiol 172.8.

Using the above procedures, but employing, in place of the protected thiol 172.6, different thiol 172.1, the corresponding products 172.4 are obtained.

Scheme 173 illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached to the phenyl ring by means of an alkoxy group. In this procedure, a dimethoxy aminophenol 173.1 is converted, via the diazo compound, into the corresponding thiophenol 173.2. The thiol group is then protected, and the product 173.3 is alkylated, as described in Scheme 168, with a dialkyl bromoalkyl phosphonate 173.4.

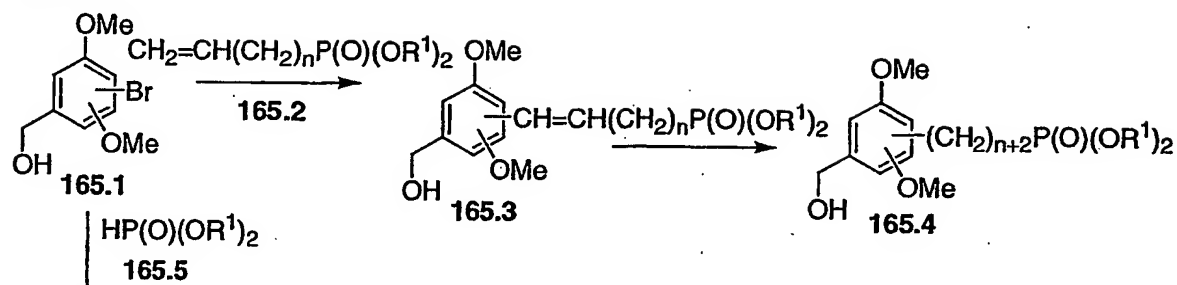
Deprotection of the product 173.5 then affords the thiophenol 173.6.

For example, 5-amino-2,3-dimethoxyphenol 173.7, prepared as described in WO 9841512, is converted by diazotization, as described above, into the thiophenol 173.8, and the product is protected by reaction with one molar equivalent of benzoyl chloride in pyridine, to yield the S-benzoyl product 173.9. The latter compound is then reacted, in dimethylformamide solution at 80°C, with a dialkyl bromoethyl phosphonate 173.10 (Aldrich) and cesium carbonate, to produce the ethoxyphosphonate 173.11. Deprotection, as described in Scheme 171, then yields the thiol 173.12.

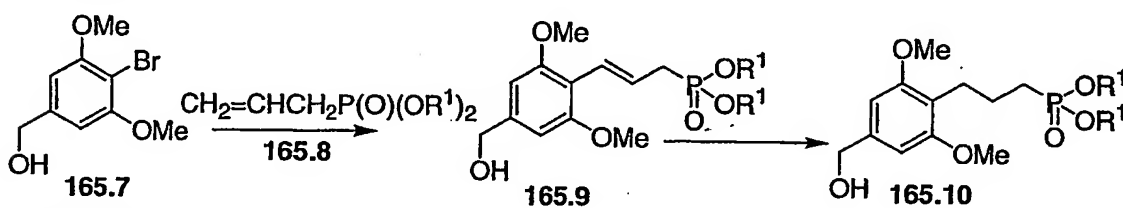
Using the above procedures, but employing, in place of the thiol 173.8, different thiol 173.2, and/or different bromoalkyl phosphonates 173.4, the corresponding products 173.6 are obtained.

Scheme 165

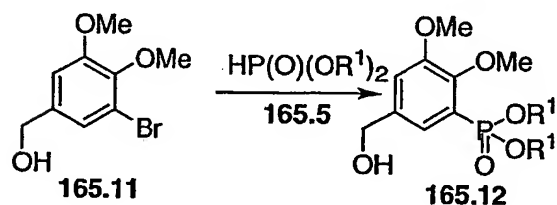
Method



Example 1

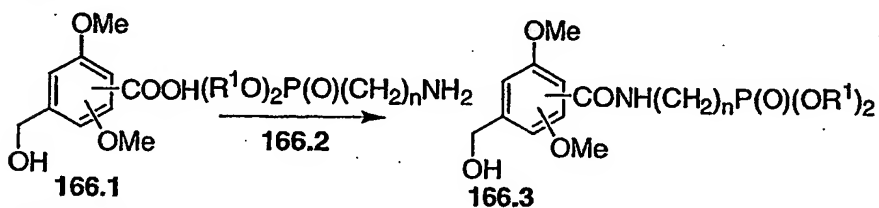


Example 2

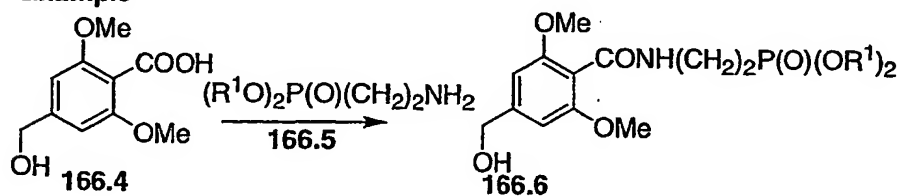


Scheme 166

Method

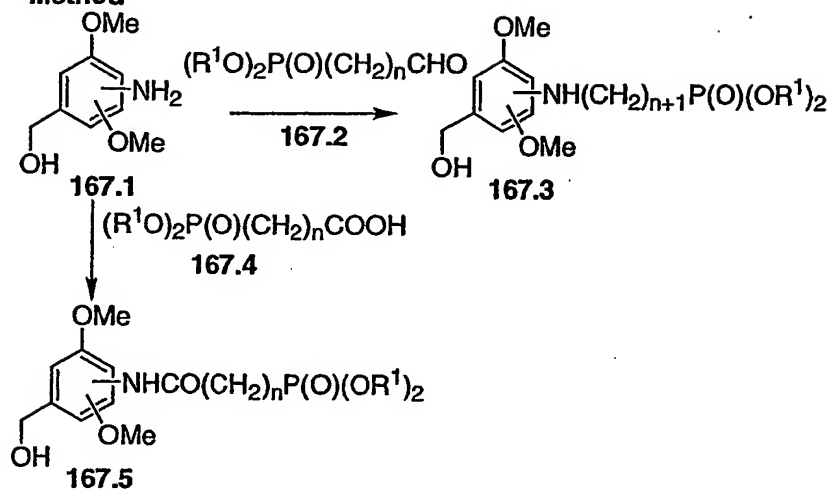


Example

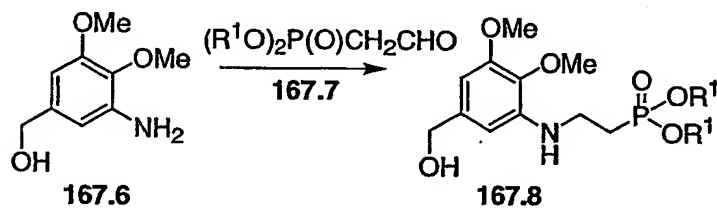


Scheme 167

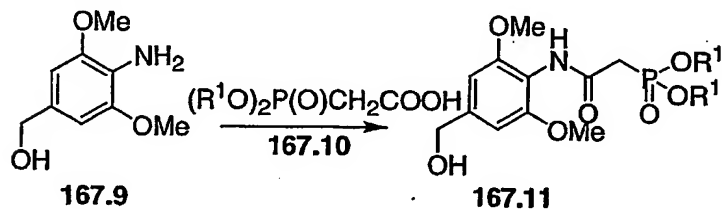
Method



Example 1

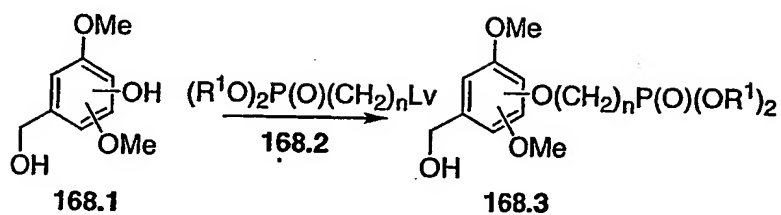


Example 2

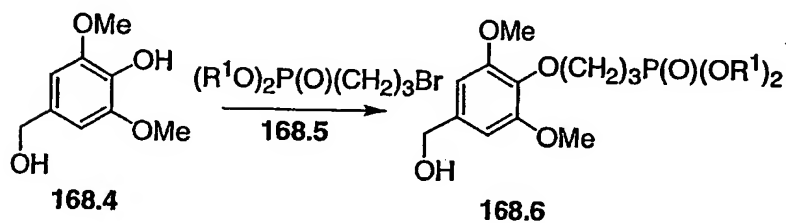


Scheme 168

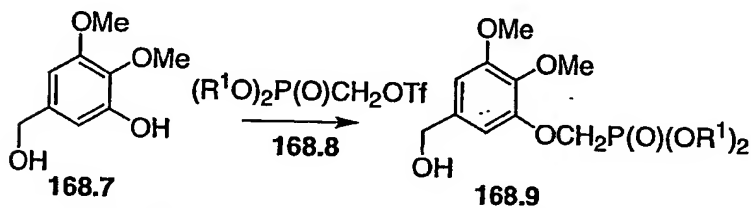
Method



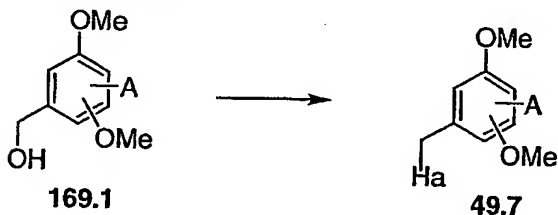
Example 1



Example 2

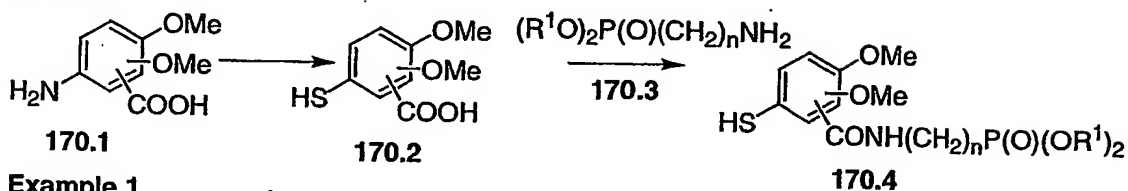


Scheme 169

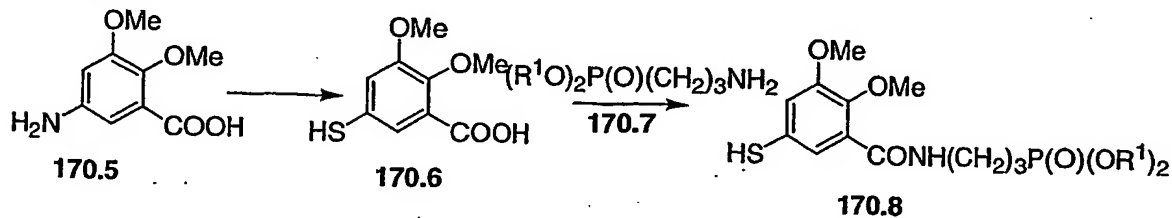


Scheme 170

Method

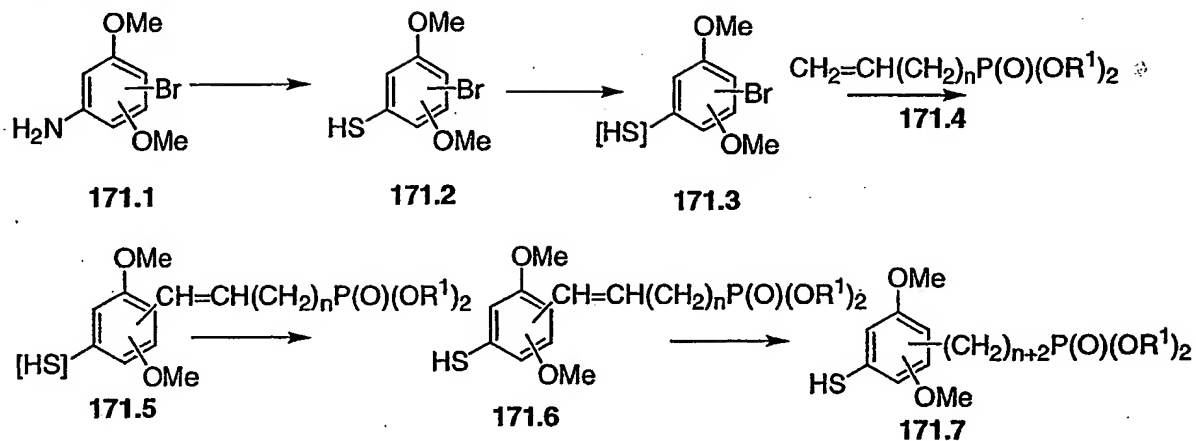


Example 1

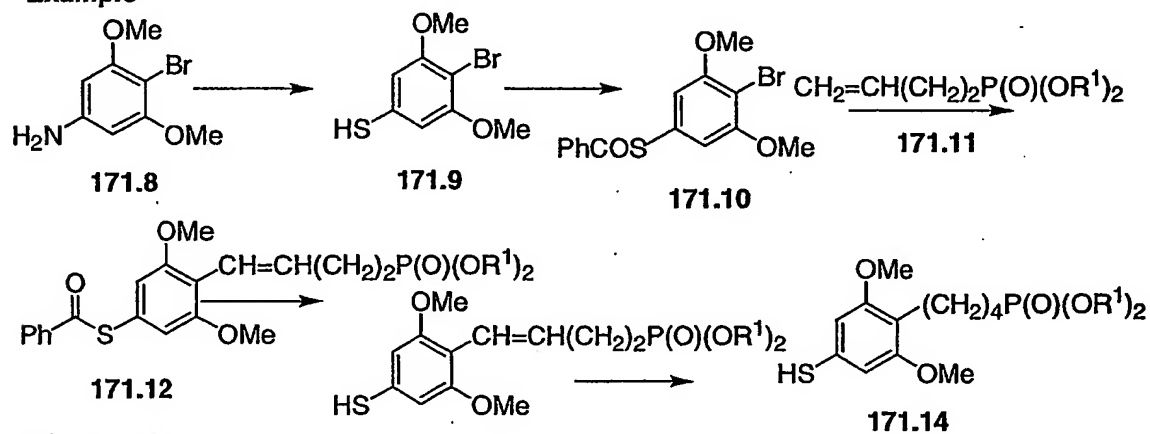


Scheme 171

Method

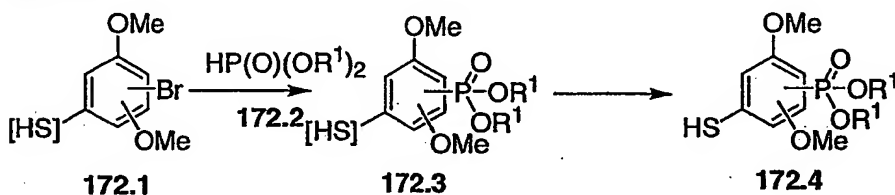


Example

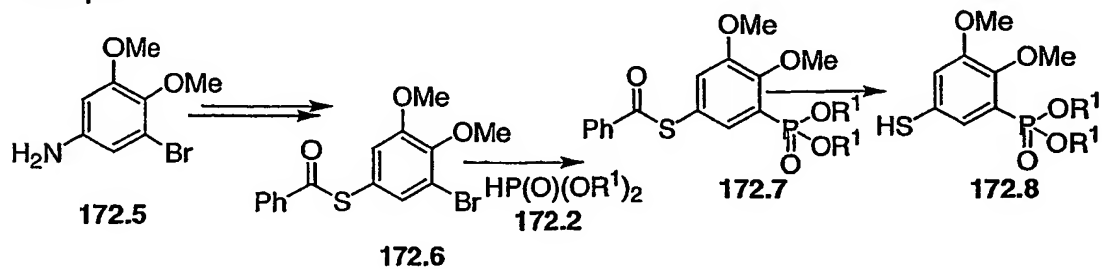


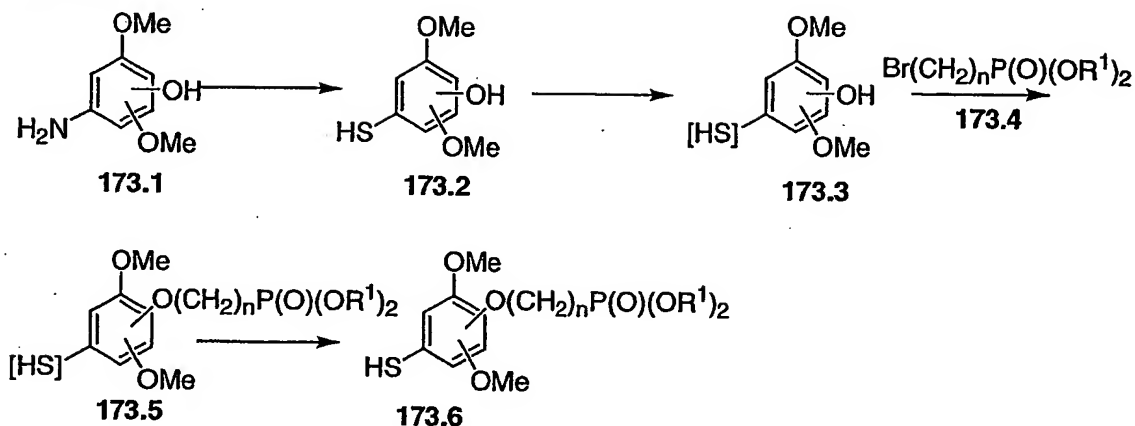
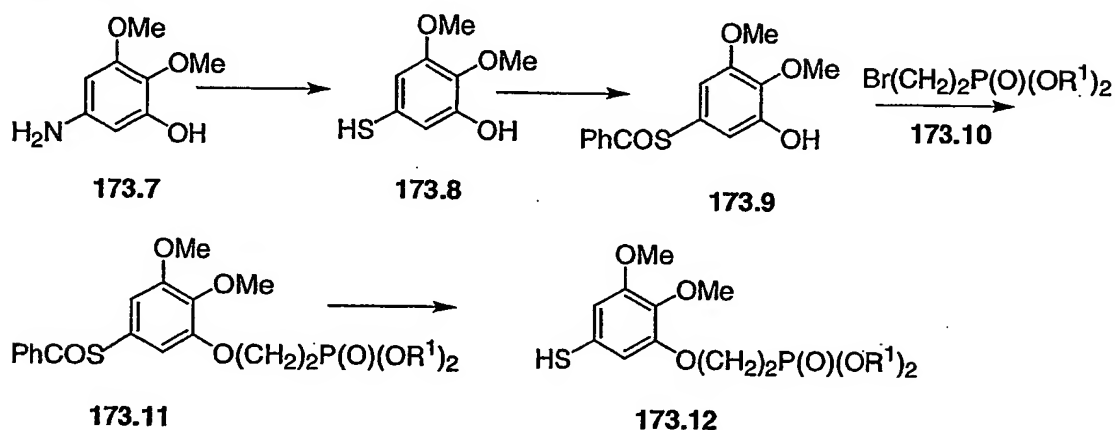
Scheme 172

Method



Example



Scheme 173**Method****Example**

5 Preparation of ethanolamine derivatives 29.1 incorporating phosphonate groups.

Schemes 174 - 178 illustrate the preparation of the ethanolamine derivatives 29.1 which are employed in the preparation of the phosphonate esters 18 and 8.

- 10 Scheme 174 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkyl chain. In this procedure, ethanolamine 174.1 is protected to give the derivative 174.2. The product is then reacted with a dialkyl alkyl phosphonate 174.3 in which the alkyl group incorporates a leaving group Lv. The alkylation

reaction is performed in a polar organic solvent such as acetonitrile or dimethylformamide, in the presence of a strong base such as sodium hydride or lithium hexamethyldisilazide, to afford the ether product 174.4. The protecting group is then removed to yield the amine 174.5. The protection and deprotection of amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309. The amino compound 174.5 is then coupled, as described in Scheme 1, with the aminoacid 174.6, to give the amide 174.7.

For example, equimolar amounts of phthalimide and ethanolamine are reacted in toluene at 70°C, as described in J. Org. Chem., 43, 2320, 1978, to prepare the phthalimido derivative 174.8, in which Phth is phthalimido. The product is then reacted, in tetrahydrofuran, with sodium hydride and an equimolar amount of a dialkyl trifluoromethylsulfonyloxymethyl phosphonate 174.9, the preparation of which is described in Tet. Lett., 1986, 27, 1497, to afford the ether product 174.10. The phthalimido group is then removed by treatment of the product 174.10 with ethanolic hydrazine at ambient temperature, as described in J. Org. Chem., 43, 2320, 1978, to yield the amine 174.11. The product is then coupled, in the presence of dicyclohexylcarbodiimide, with the aminoacid 174.6, to yield the amide 174.12. Using the above procedures, but employing, in place of the methylphosphonate 174.9, different alkylphosphonates 174.3, the corresponding products 174.7 are obtained.

Scheme 175 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkylene chain incorporating a nitrogen. In this procedure, ethanolamine 174.1 and the aminoacid 174.6 are coupled, as described in Scheme 1, to form the amide 175.1. The product is then alkylated with a bromoalkyl aldehyde 175.2 to yield the ether 175.3. The alkylation reaction is performed in a polar organic solvent such as acetonitrile or dioxan, in the presence of a strong base such as potassium tert. butoxide or sodium hydride, at about 60°C. The aldehyde product is then reacted, under reductive amination conditions, as described in Scheme 135, with a dialkyl aminoalkyl phosphonate 175.4, to produce the amine product 175.5.

For example, the amide 175.1 is reacted, as described above, with bromoacetaldehyde 175.6, to afford the ether 175.7. The product is then reacted in ethanol with a dialkyl aminoethyl phosphonate 175.8, (Aurora) and sodium triacetoxyborohydride, to yield the amine 175.9.

Using the above procedures, but employing, in place of the bromoacetaldehyde 175.6, different bromoalkyl aldehydes 175.2, and/or different aminoalkyl phosphonates 175.4, the corresponding products 175.5 are obtained.

- 5 Scheme 176 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of a phenyl ring. In this procedure, bromoethylamine 176.1 and the aminoacid 174.6 are coupled, as described in Scheme 1, to afford the amide 176.2. The product is then reacted with the dialkyl hydroxyalkyl-substituted phenylphosphonate 176.3 to prepare the ether 176.4. The alkylation reaction is performed in a polar organic solvent such as dimethyl sulfoxide or dioxan, in the presence of a base such as lithium
- 10 bis(trimethylsilyl)amide, sodium hydride or lithium piperidide. For example, the amide 176.2 is reacted in dimethylformamide with a dialkyl 4-(2-hydroxyethyl)phenyl phosphonate 176.5, prepared as described in J. Am. Chem. Soc., 1996, 118, 5881, and sodium hydride, to furnish the ether product 176.6.
- 15 Using the above procedures, but employing, in place of the hydroxyethyl phenylphosphonate 176.5, different phosphonates 176.3, the corresponding products 176.4 are obtained.

- Scheme 177 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkylene chain. In this procedure, the aminoacid 174.6 is
- 20 coupled with a bromoalkoxy-substituted ethylamine 177.1 to give the amide 177.2. The product is then subjected to an Arbuzov reaction with a trialkyl phosphite $P(OR^1)_3$. In this procedure, described in Handb. Organophosphorus Chem., 1992, 115, the reactants are heated together at ca. 100°C to afford the product 177.4.

- For example, the aminoacid 174.6 is coupled, as described in Scheme 1, in acetonitrile solution containing dicyclohexylcarbodiimide, with 2-bromoethoxyethylamine 177.5, prepared as
- 25 described in Vop. Khim. Tekh., 1974, 34, 6, to produce the amide 177.6. The product is then heated at 120°C with excess trialkyl phosphite 177.3, to afford the phosphonate 177.7. Using the above procedures, but employing, in place of the bromoethoxyethylamine 177.5, different bromoalkyl ethylamines 177.1, the corresponding products 177.4 are obtained.

30

Scheme 178 depicts the preparation of the amines 29.1. The BOC-protected ethanolamine derivatives 178.1, in which the group A is either the substituent link- $P(O)(OR^1)_2$, or a

precursor thereto, prepared as described in Schemes 174 - 177, are deprotected to afford the amines 29.1. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection is effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride in ethyl acetate, or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preparation of the chroman phosphonate esters 33.1.

Schemes 179 - 181a illustrate the preparation of the chroman phosphonate esters 33.1 which are employed in the preparation of the phosphonate esters 17 and 9.

Scheme 179 depicts the preparation of (2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazol-4-yl)-methanol, 179.6, 2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazole-4-carbaldehyde, 179.7, and 2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazole-4-carboxylic acid, 179.8, which are used in the preparation of the phosphonates 33.1. In this procedure, (2H-chromen-2-yl)-methanol 179.1, prepared as described in J. Chem. Soc., (D), 344, 1973, is converted, as described above, (Scheme 1) into the tert. butyldimethylsilyl ether 179.2. The product is then reacted, as described in J. Het. Chem., 1975, 12, 1179, with silver cyanate and iodine in ether, so as to afford the addition product 179.3. This compound is then heated on methanol to yield the carbamate derivative 179.4. The latter compound is heated in xylene at reflux, as described in J. Het. Chem., 1975, 12, 1179, to produce the oxazoline derivative 179.5. The silyl group is then removed by reaction with tetrabutylammonium fluoride in tetrahydrofuran to yield the carbinol 179.6. The carbinol is oxidized to produce the aldehyde 179.7. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. The alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, dimethyl sulfoxide/acetic anhydride or dimethyl sulfoxide-dicyclohexyl carbodiimide. The reaction is conducted in an inert aprotic solvent such as dichloromethane or toluene. The aldehyde 179.7 is oxidized to the carboxylic acid 179.8. The oxidation of aldehydes to carboxylic acids is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 838ff. The conversion is effected by treatment with oxidizing agents such as potassium permanganate,

ruthenium tetroxide, chromium trioxide in acetic acid, or, preferably, by the use of silver oxide, as described in J. Am. Chem. Soc., 73, 2590, 1951.

Scheme 180 illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of an aminoalkyl chain. In this procedure, the aldehyde 179.7 is reacted, under reductive amination conditions, as described in Scheme 175, with a dialkyl aminoalkyl phosphonate 180.1, to give the amine 180.2. The oxazoline group is then hydrolyzed, for example by reaction with aqueous potassium hydroxide, as described in J. Het. Chem., 1975, 12, 1179, to yield the hydroxyamine 180.3.

For example, the aldehyde 179.7 is reacted in ethanol with a dialkyl aminomethyl phosphonate 180.4, (Interchim) and sodium triacetoxymethylborohydride, to produce the amine 180.5. The oxazoline is then hydrolyzed, as described above, to afford the hydroxyamine 180.6. Using the above procedures, but employing, in place of the aminomethyl phosphonate 180.4, different phosphonates 180.1, the corresponding products 180.3 are obtained.

Scheme 181 illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of an amide group. In this procedure, the carboxylic acid 179.8 is coupled, as described in Scheme 1, with a dialkyl aminoalkyl phosphonate 180.1, to produce the amide 181.1. Hydrolysis of the oxazoline group, as described above, then yields the hydroxyamine 181.2.

For example, the carboxylic acid 179.8 is coupled with a dialkyl aminopropyl phosphonate 181.3, (Acros) to afford the amide 181.4, which is then hydrolyzed to give the hydroxyamine 181.5.

Using the above procedures, but employing, in place of the aminopropyl phosphonate 181.3, different phosphonates 180.1, the corresponding products 181.2 are obtained.

Scheme 181a illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of a thioalkyl group. In this procedure, the carbinol 179.6 is converted into the bromo derivative 181a.1. The conversion of alcohols into bromides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 356ff. For example, the alcohol is reacted with triphenyl phosphine and carbon tetrabromide, trimethylsilyl bromide, thionyl bromide and the like. The bromo compound is

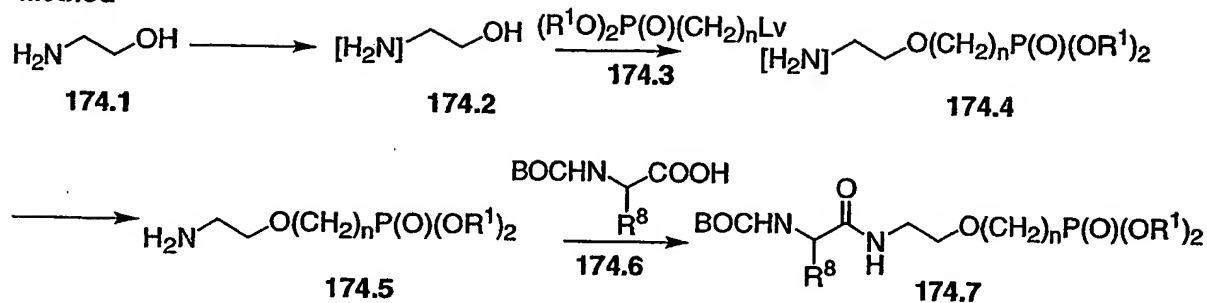
then reacted with a dialkyl thioalkyl phosphonate **181a.2** to effect displacement of the bromide and formation of the thioether **181a.3**. The reaction is performed in a polar organic solvent such as ethanol in the presence of a base such as potassium carbonate. Removal of the isoxazoline group then produces the hydroxyamine **181a.4**.

- 5 For example, the bromo compound **181a.1** is reacted in ethanol with a dialkyl thioethyl phosphonate **181a.5**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, and potassium carbonate, to yield the thioether product **181a.6**. Hydrolysis, as described above, then affords the hydroxyamine **181a.7**.

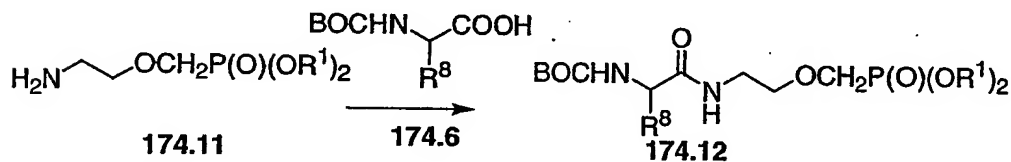
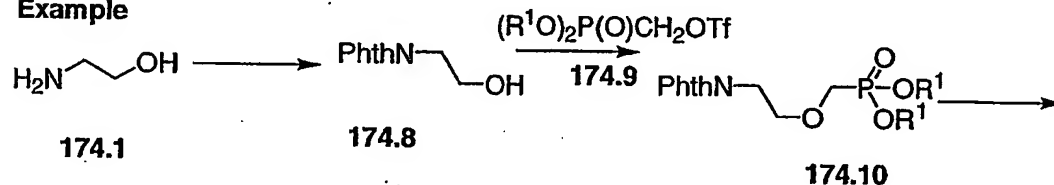
- Using the above procedures, but employing, in place of the thioethyl phosphonate **181a.5**,
10 different phosphonates **181a.2**, the corresponding products **181a.4** are obtained.

Scheme 174

Method

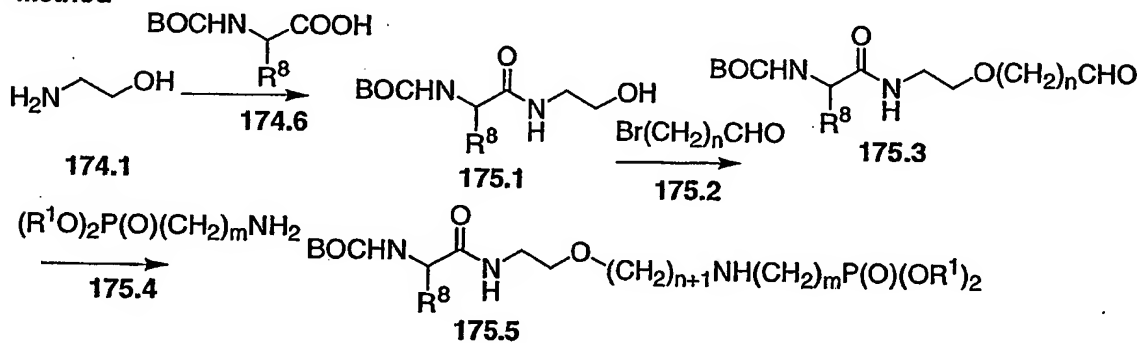


Example

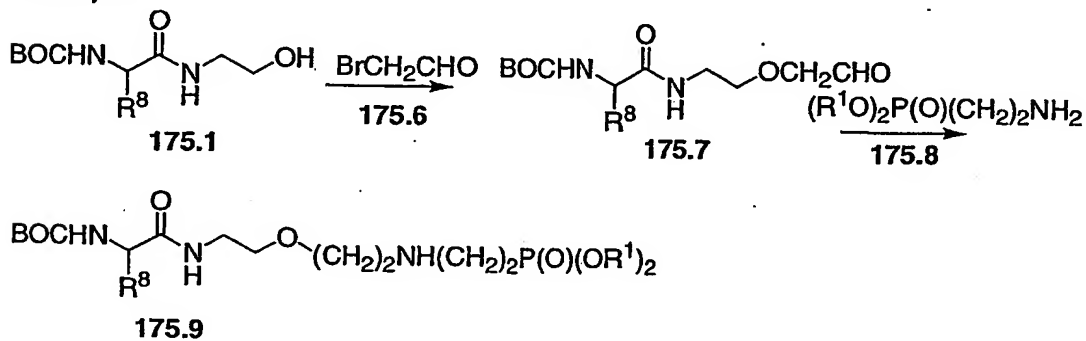


Scheme 175

Method

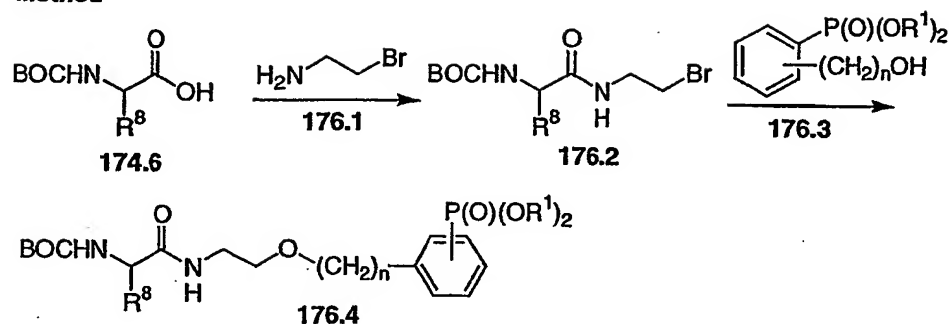


Example

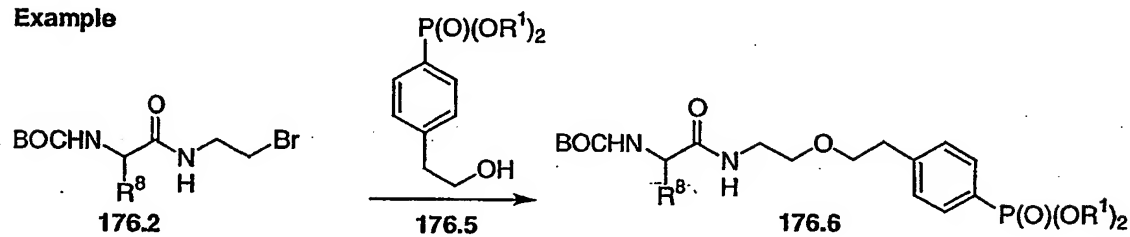


Scheme 176

Method

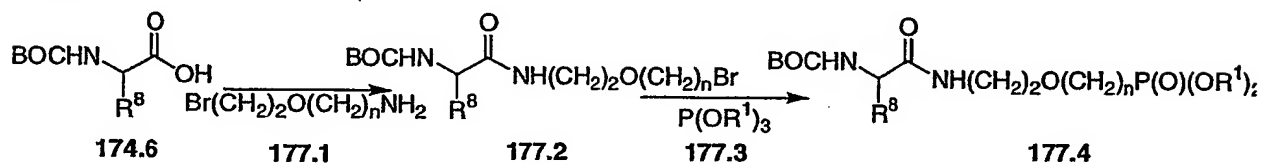


Example

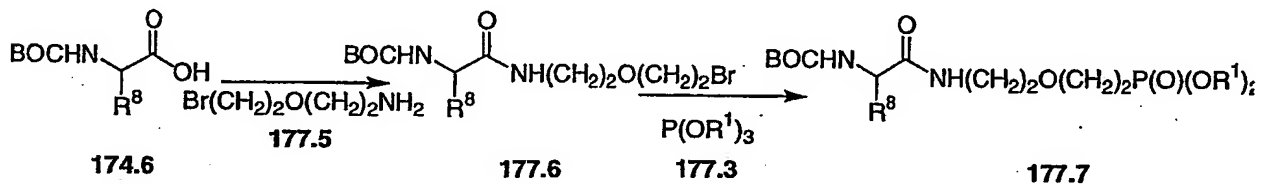


Scheme 177

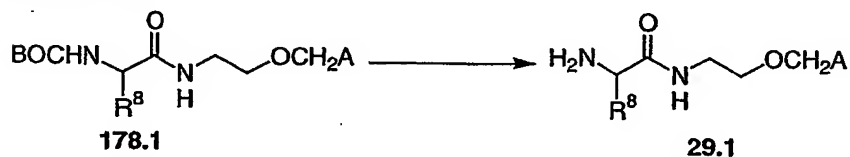
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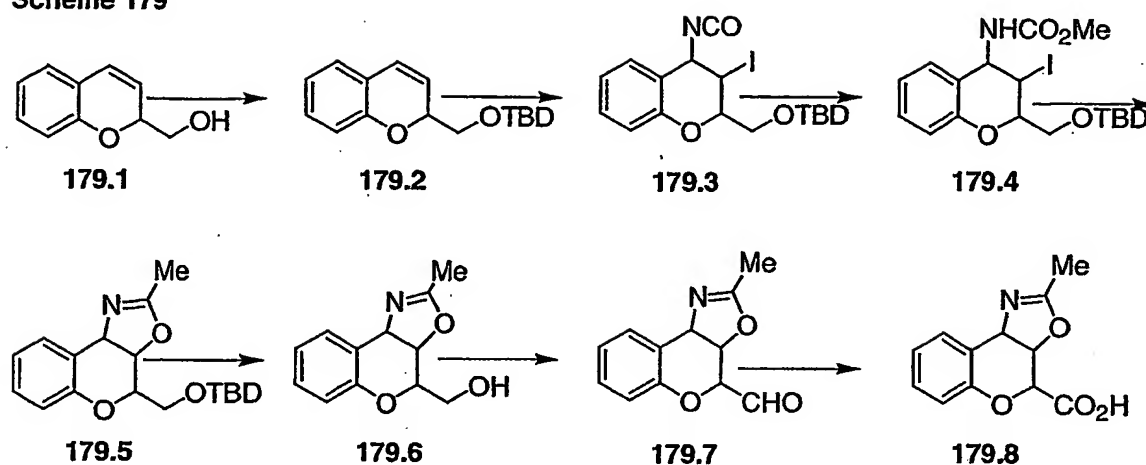
Example



Scheme 178

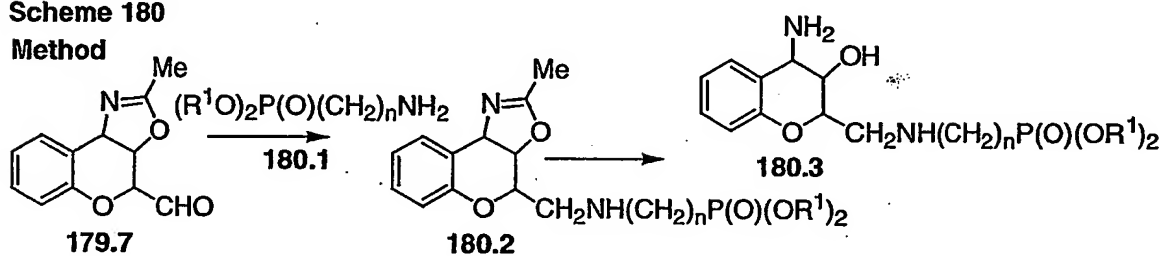


Scheme 179

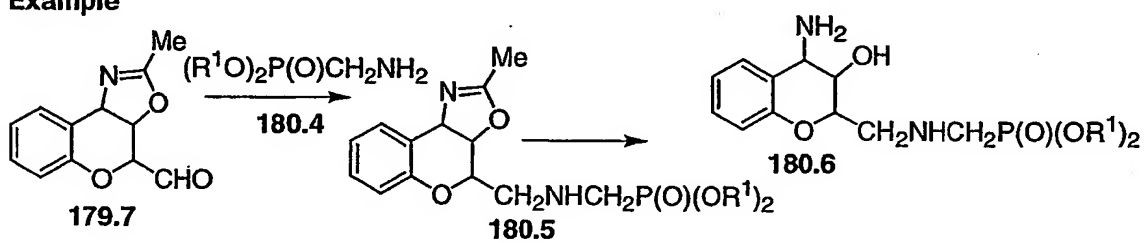


Scheme 180

Method

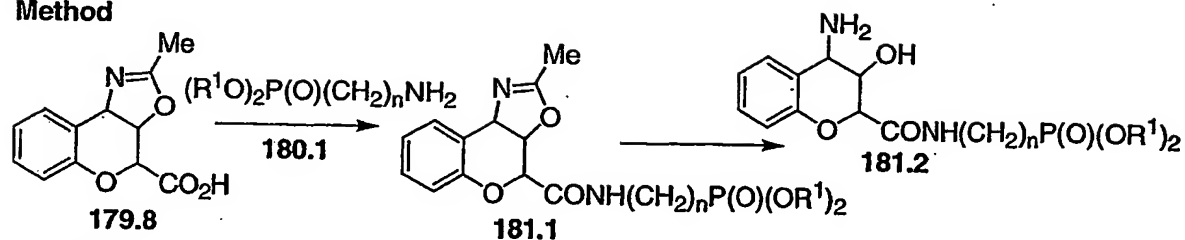


Example

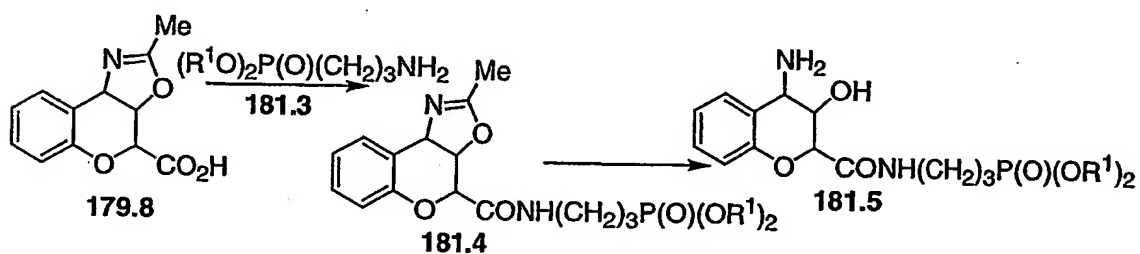


Scheme 181

Method

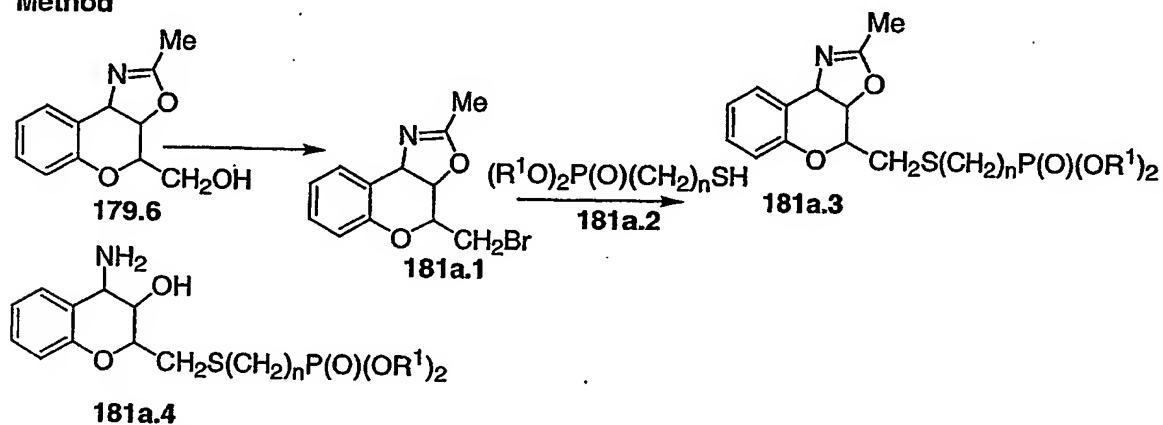


Example

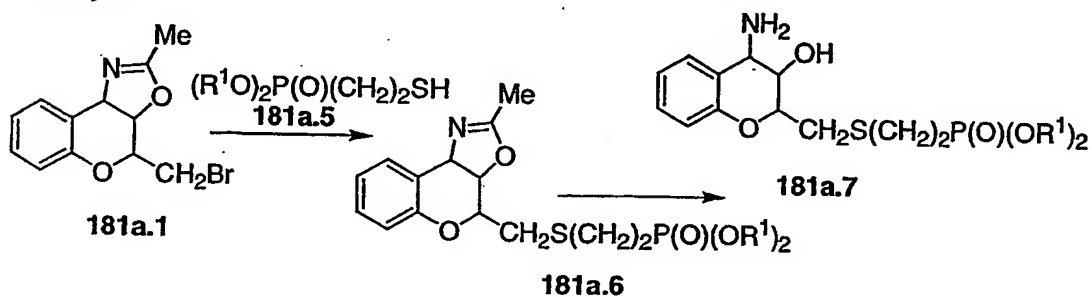


Scheme 181a

Method



Example



Preparation of phenylalanine derivatives 37.1 incorporating phosphonate moieties.

Schemes 182 - 185 illustrate the preparation of phosphonate-containing phenylalanine derivatives 37.1 which are employed in the preparation of the intermediate phosphonate esters 10 and 19.

5

Scheme 182 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives 182.1.

- 10 In this procedure, a hydroxy or mercapto-substituted phenylalanine is converted into the benzyl ester 182.2. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion is effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a
- 15 benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester 182.2 is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, suitable protecting groups for phenols and thiophenols include tert-butyldimethylsilyl or tert-
- 20 butyldiphenylsilyl. Thiophenols are also protected as S-adamantyl groups, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. The protected hydroxy- or mercapto ester 182.3 is then converted into the BOC derivative 182.4. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in Protective Groups in Organic
- 25 Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride, in a solvent such as tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl groups are removed by treatment with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.
- 30 The resultant phenol or thiophenol 182.5 is then reacted under various conditions to provide protected phenylalanine derivatives 182.9, 182.10 or 182.11, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

In this step, the phenol or thiophenol **182.5** is reacted with a dialkyl bromoalkyl phosphonate **182.6** to afford the ether or thioether product **182.9**. The alkylation reaction is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate. The reaction is performed at from ambient temperature to ca. 80°C, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product **182.9**. Deprotection of the benzyl ester group, for example by means of catalytic hydrogenation over a palladium catalyst, then yields the carboxylic acid **182.12**. The benzyl esters **182.10** and **182.11**, the preparation of which is described above, are similarly deprotected to produce the corresponding carboxylic acids.

For example, as illustrated in Scheme **182**, Example **1**, a hydroxy-substituted phenylalanine derivative such as tyrosine, **182.13** is converted, as described above, into the benzyl ester **182.14**. The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether **182.15**. This compound is then converted, as described above, into the BOC derivative **182.16**. The silyl protecting group is removed by treatment of the silyl ether **182.16** with a tetrahydrofuran solution of tetrabutylammonium fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol **182.17**. The latter compound is then reacted in dimethylformamide at ca. 60°C, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **182.18** (Aldrich), in the presence of cesium carbonate, to afford the alkylated product **182.19**. Debenzylation then produces the carboxylic acid **182.20**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **182.13**, different hydroxy or thio-substituted phenylalanine derivatives **182.1**, and/or different bromoalkyl phosphonates **182.6**, the corresponding ether or thioether products

182.12 are obtained.

Alternatively, the hydroxy or mercapto-substituted phenylalanine derivative **182.5** is reacted with a dialkyl hydroxymethyl phosphonate **182.7** under the conditions of the Mitsunobu reaction, to afford the ether or thioether compounds **182.10**. The preparation of aromatic ethers and thioethers by means of the Mitsunobu reaction is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic

solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **182.10**.

For example, as shown in Scheme **182**, Example 2, 3-mercaptophenylalanine **182.21**, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester **182.22**.

5 The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether **182.23**. This compound is then converted into the BOC-protected derivative **182.24**. The 4-methoxybenzyl group is then removed by the reaction of the thioether **182.24** with mercuric trifluoroacetate and anisole in
10 trifluoroacetic acid, as described in J.Org. Chem., 52, 4420, 1987, to afford the thiol **182.25**. The latter compound is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl hydroxymethyl phosphonate **182.7**, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product **182.26**. The benzyl ester protecting group is then removed to afford the carboxylic acid **182.27**.

15 Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative **182.21**, different hydroxy or mercapto-substituted phenylalanines **182.1**, and/or different dialkyl hydroxymethyl phosphonates **182.7**, the corresponding products **182.10** are obtained.

Alternatively, the hydroxy or mercapto-substituted protected phenylalanine derivative **182.5** is
20 reacted with an activated derivative of a dialkyl hydroxymethylphosphonate **182.8** in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products **182.11**.

For example, as illustrated in Scheme **182**, Example 3, 3-hydroxyphenylalanine **182.28** (Fluka)
25 is converted, using the procedures described above, into the protected compound **182.29**. The latter compound is reacted, in dimethylformamide at ca. 50°C, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate **182.30**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product **182.31**. Debenzylation then produces the carboxylic acid **182.32**.

30 Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **182.28**, different hydroxy or mercapto-substituted phenylalanines **182.1**, and/or

different dialkyl trifluoromethanesulfonyloxymethylphosphonates **182.8**, the corresponding products **182.11** are obtained.

Scheme 183 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted protected phenylalanine derivative **183.3** and a dialkyl aminoalkylphosphonate **183.4**.

In this procedure, a hydroxymethyl-substituted phenylalanine **183.1** is converted, as described above, into the BOC protected benzyl ester **183.2**. The latter compound is then oxidized to afford the corresponding aldehyde **183.3**. The conversion of alcohols to aldehydes is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the

aldehyde product **183.3**. For example, the carbinol **183.2** is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in *J. Org. Chem.*, 43, 2480, 1978, to yield the aldehyde **183.3**. This compound is reacted with a dialkyl aminoalkylphosphonate **183.4** in the presence of a suitable reducing agent to afford the amine product **183.5**. The preparation of amines by means of reductive amination procedures is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in *Advanced Organic Chemistry, Part B*, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a

Lewis acid, such as titanium tetraisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990. The benzyl protecting group is then removed to prepare the carboxylic acid **183.6**.

For example, 3-(hydroxymethyl)-phenylalanine **183.7**, prepared as described in *Acta Chem. Scand. Ser. B*, 1977, B31, 109, is converted, as described above, into the formylated

derivative **183.8**. This compound is then reacted with a dialkyl aminoethylphosphonate **183.9**, prepared as described in *J. Org. Chem.*, 200, 65, 676, in the presence of sodium

cyanoborohydride, to produce the alkylated product **183.10**, which is then deprotected to give the carboxylic acid **183.11**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine 183.7, different hydroxymethyl phenylalanines 183.1, and/or different aminoalkyl phosphonates 183.4, the corresponding products 183.6 are obtained.

- 5 Scheme 184 depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine 184.1 is converted, as described above, (Scheme 182) into the protected derivative 184.2. The product is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite 184.3 to produce the phosphonate ester 184.4. The preparation of
10 arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The product is then deprotected to afford the carboxylic acid 184.5.

- For example, 3-bromophenylalanine 184.6, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme 182) into the protected compound 184.7. This
15 compound is then reacted, in toluene solution at reflux, with diethyl phosphite 184.8, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 184.9. Debenzylation then yields the carboxylic acid 184.10.

- Using the above procedures, but employing, in place of 3-bromophenylalanine 184.6, different
20 bromophenylalanines 184.1, and/or different dialkylphosphites 184.3, the corresponding products 184.5 are obtained.

- Scheme 185 depicts the preparation of the aminoacid derivative 37.1 which is employed in the preparation of the phosphonate esters 10 and 19. In this procedure, the BOC-protected
25 phenylalanine derivatives 185.1, in which the substituent A is the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor group, the preparation of which is described in Schemes 182 – 184, is converted into the esters or amides 185.2 in which R^9 is morpholino or alkoxy. The transformation is accomplished by coupling the acid, as described in Scheme 1, with morpholine or an alkanol in the presence of a carbodiimide. The product 185.2 is then deprotected to afford the free
30 amine 185.3, for example as described in Scheme 3. The amine 185.3 is then coupled, as described in Scheme 1, with the aminoacid 174.6, to give the amide 185.4. The BOC group is then removed, as described in Scheme 49, to produce the amine 37.1.

Preparation of the dimethoxyphenylpropionic esters 21.1 incorporating phosphonate groups.

Scheme 186 illustrates the preparation of the dimethoxyphenylpropionic acid derivatives 21.1 which are employed in the preparation of the phosphonate esters 6. In this procedure, the dimethoxybenzyl alcohol derivative 186.1, in which the substituent A is the group link-
P(O)(OR¹)₂ or a precursor group, the preparation of which is described in Schemes 165 – 168, is converted into the corresponding aldehyde 186.2. The oxidation is effected as described in Scheme 175. The aldehyde is then subjected to a Wittig reaction with methyl
triphenylphosphoranylideneacetate 138.2, as described in Scheme 138, to generate the cinnamic ester derivative 186.3. The double bond is then reduced, as described in Scheme 138, to afford the phenylpropionic ester 21.1. Alternatively, the dimethoxybenzyl bromide derivative 186.4, the preparation of which is described in Scheme 169, is reacted, as described in Scheme 138, with dimethyl malonate 186.5 to yield the malonic ester derivative 186.6, which is then transformed, as described in Scheme 138, into the ester 21.1.

Preparation of the phosphonate-containing benzyl iodides 58.1 and benzylcarbamates 125.3.

Schemes 187 - 191 illustrate methods for the preparation of the benzyl iodide derivatives 58.1 which are employed in the synthesis of the phosphonate esters 14, and of the benzyl carbamates 125.3 which are employed in the preparation of the phosphonate esters 22.

Scheme 187 illustrates the preparation of benzaldehyde phosphonates 187.3 in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde 187.1 is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate 187.2, under reductive amination conditions, as describe above in Scheme 135, to yield the phosphonate product 187.3.

For example, benzene-1,3-dialdehyde 187.4 is reacted with a dialkyl aminopropyl phosphonate 187.5, (Acros) and sodium triacetoxyborohydride, to afford the product 187.6.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde 187.4, different benzene dialdehydes 187.1, and/or different phosphonates 187.2, the corresponding products 187.3 are obtained.

5 Scheme 188 illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated carbon chain. In this procedure, a bromobenzaldehyde 188.1 is coupled, under palladium catalysis as described in Scheme 150, with a dialkyl alkenylphosphonate 188.2, to afford the alkenyl phosphonate 188.3. Optionally, the product is reduced, as described in Scheme 150, to afford the saturated
10 phosphonate ester 188.4. Alternatively, the bromobenzaldehyde is coupled, as described in Scheme 144, with a dialkyl phosphite 188.5 to afford the formylphenylphosphonate 188.6. For example, as shown in Example 1, 3-bromobenzaldehyde 188.7 is coupled with a dialkyl propenylphosphonate 188.8 (Aldrich) to afford the propenyl product 188.9. Optionally, the product is reduced, as described in Scheme 150, to yield the propyl phosphonate 188.10.

15 Using the above procedures, but employing, in place of 3-bromobenzaldehyde 188.7, different bromobenzaldehydes 188.1, and/or different alkenyl phosphonates 188.2, the corresponding products 188.3 and 188.4 are obtained.

Alternatively, as shown in Example 2, 4-bromobenzaldehyde 188.11 is coupled, as described in Scheme 144, with a dialkyl phosphite 188.5 to afford the 4-formylphenyl phosphonate
20 product 188.12.

Using the above procedures, but employing, in place of 4-bromobenzaldehyde 188.11, different bromobenzaldehydes 188.1, the corresponding products 188.6 are obtained.

Scheme 189 illustrates the preparation of formylphenyl phosphonates in which the
25 phosphonate moiety is attached by means of alkylene chains incorporating two heteroatoms O, S or N. In this procedure, a formyl phenoxy, phenylthio or phenylamino alkanol, alkanethiol or alkylamine 189.1 is reacted with an equimolar amount of a dialkyl haloalkyl phosphonate 189.2, to afford the phenoxy, phenylthio or phenylamino phosphonate product 189.3. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or
30 acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile 189.1. In cases in which Y is O, a strong base such as sodium hydride or lithium

hexamethyldisilazide is employed. In cases in which Y is S or N, a base such as cesium carbonate or dimethylaminopyridine is employed.

For example, 2-(4-formylphenylthio)ethanol **189.4**, prepared as described in *Macromolecules*, 1991, 24, 1710, is reacted in acetonitrile at 60°C with one molar equivalent of a dialkyl

5 iodomethyl phosphonate **189.5**, (Lancaster) to give the ether product **189.6**.

Using the above procedures, but employing, in place of the carbinol **189.4**, different carbinols, thiols or amines **189.1**, and/or different haloalkyl phosphonates **189.2**, the corresponding products **189.3** are obtained.

10 Scheme **190** illustrates the preparation of formylphenyl phosphonates in which the phosphonate group is linked to the benzene ring by means of an aromatic or heteroaromatic ring. In this procedure, a formylbenzeneboronic acid **190.1** is coupled, in the presence of a palladium catalyst, with one molar equivalent of a dibromoarene, **190.2**, in which the group Ar is an aromatic or heteroaromatic group. The coupling of aryl boronates with aryl bromides to

15 afford diaryl compounds is described in *Palladium Reagents and Catalysts*, by J. Tsuji, Wiley 1995, p. 218. The components are reacted in a polar solvent such as dimethylformamide in the presence of a palladium(0) catalyst and sodium bicarbonate. The product **190.3** is then coupled, as described above (Scheme **144**) with a dialkyl phosphite **190.4** to afford the phosphonate **190.5**.

20 For example, 4-formylbenzeneboronic acid **190.6** is coupled with 2,5-dibromothiophene **190.7** to yield the phenylthiophene product **190.8**. This compound is then coupled with the dialkyl phosphite **190.4** to afford the thienyl phosphonate **190.9**.

Using the above procedures, but employing, in place of dibromothiophene **190.7**, different dibromoarenes **190.2**, and/or different formylphenyl boronates **190.1**, the corresponding

25 products **190.5** are obtained.

Scheme **191** illustrates the preparation of the benzyl carbamates **125.3** and the benzyl iodides **58.1**, which are employed respectively in the preparation of the phosphonate esters **22** and **4**.

In this procedure, the substituted benzaldehydes **191.1**, prepared as shown in Schemes **187** –

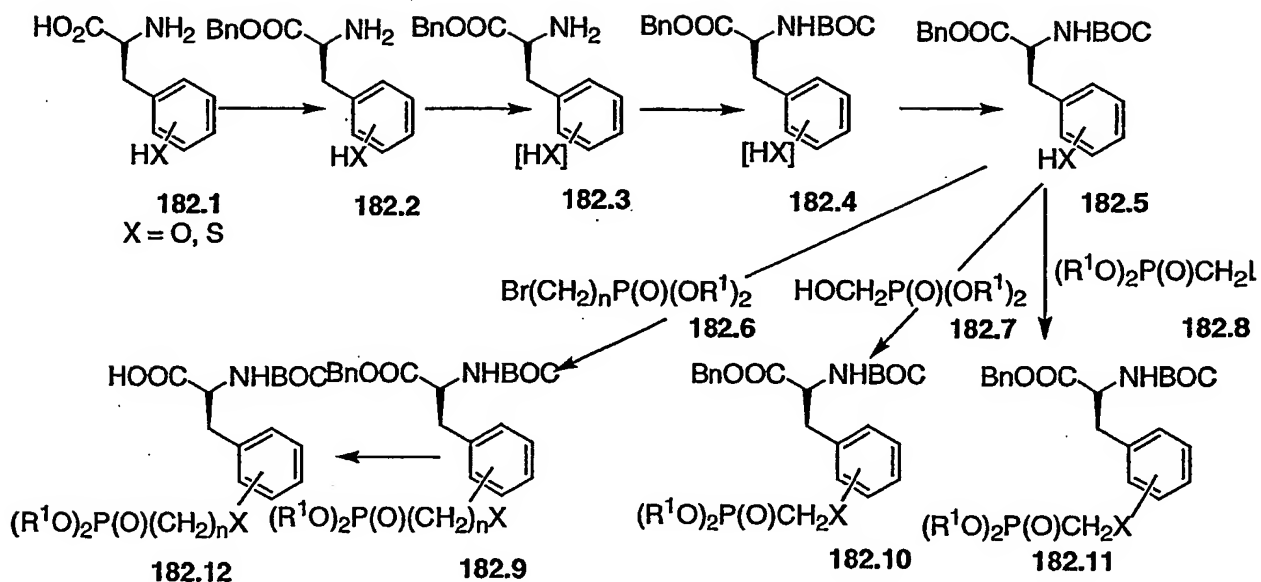
30 **190**, are converted into the corresponding benzyl alcohols **191.2**. The reduction of aldehydes to afford alcohols is described in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 527ff. The transformation is effected by the use of reducing agents such as

sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride, diisobutyl aluminum hydride and the like. The resultant benzyl alcohol is then reacted with the aminoester **191.3** to afford the carbamate **191.4**. The reaction is performed under the conditions described below,

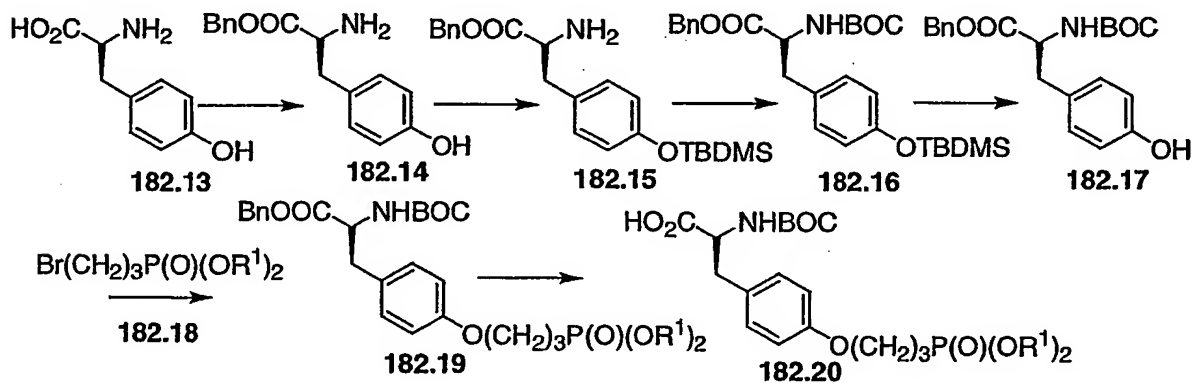
- 5 Scheme **198**. For example, the benzyl alcohol is reacted with carbonyldiimidazole to produce an intermediate benzyloxycarbonyl imidazole, and the intermediate is reacted with the aminoester **191.3** to afford the carbamate **191.4**. The methyl ester is then hydrolyzed, as described in Scheme **3**, to yield the carboxylic acid **125.3**. Alternatively, the benzyl alcohol **191.2** is converted, using the procedures of Scheme **169**, into the iodide **58.1**.

Scheme 182

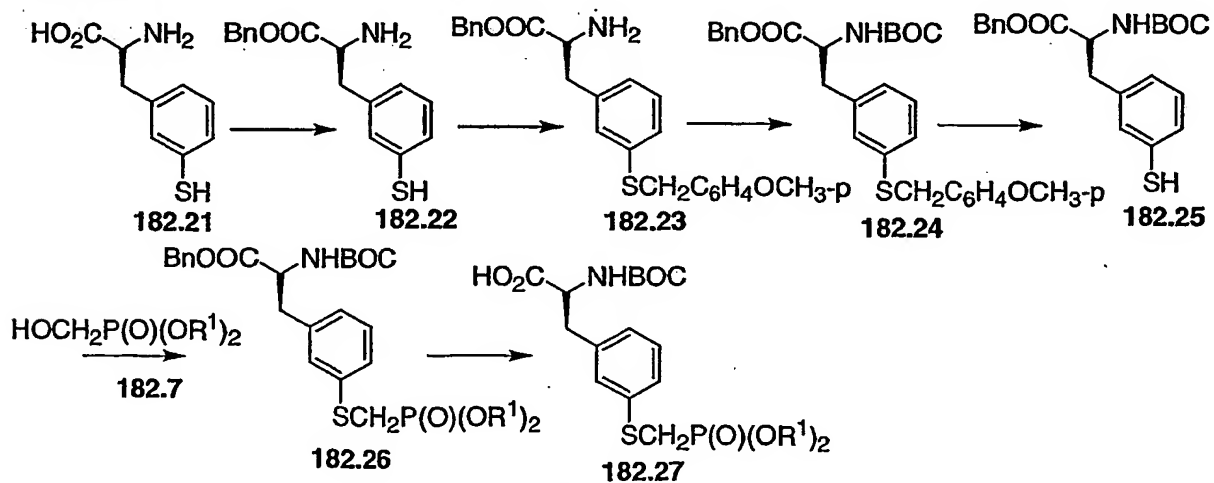
Method

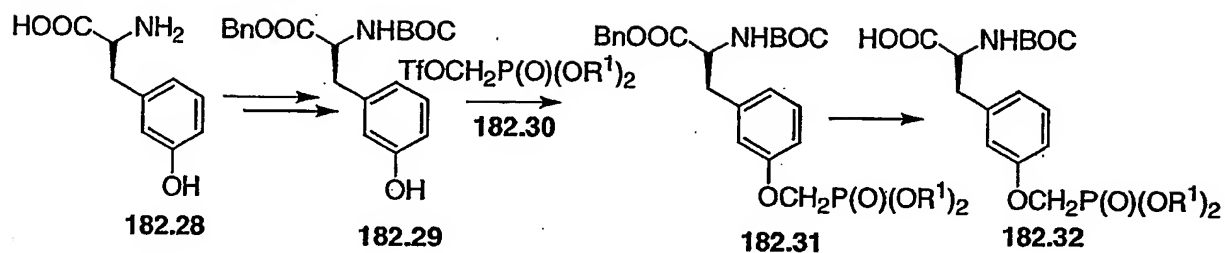
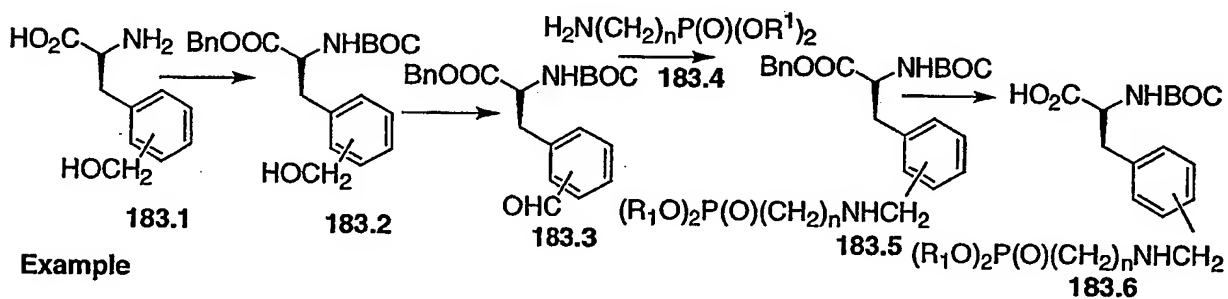
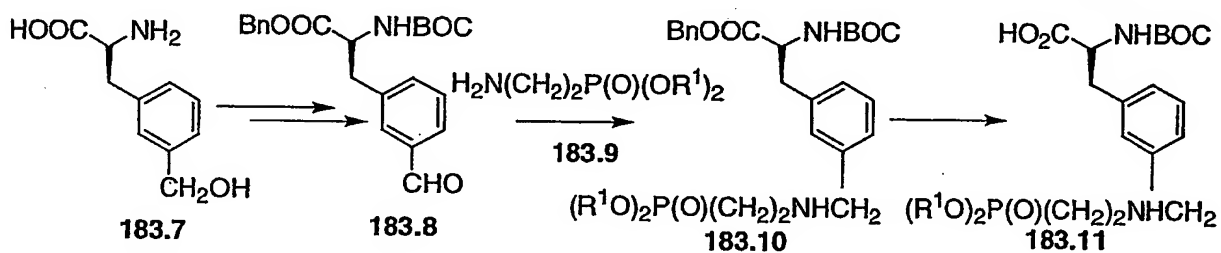
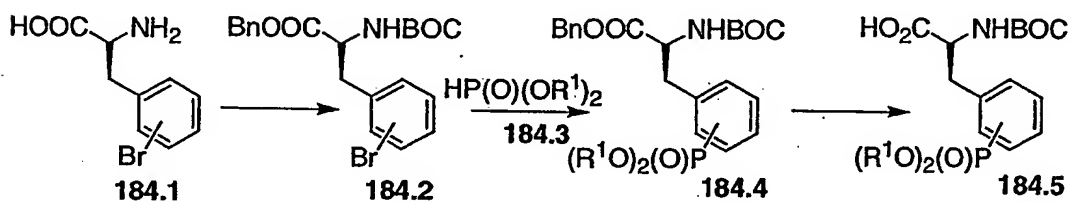
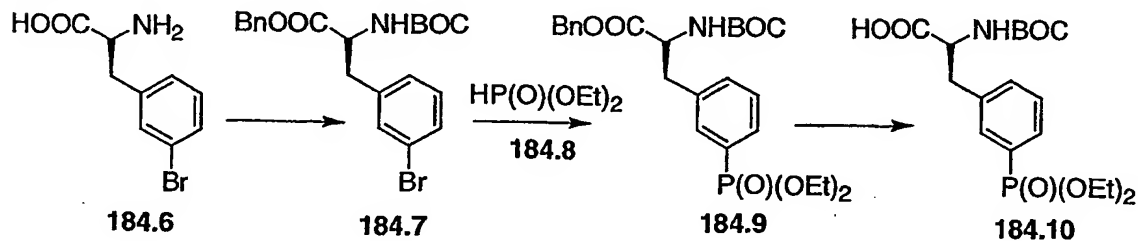


Example 1

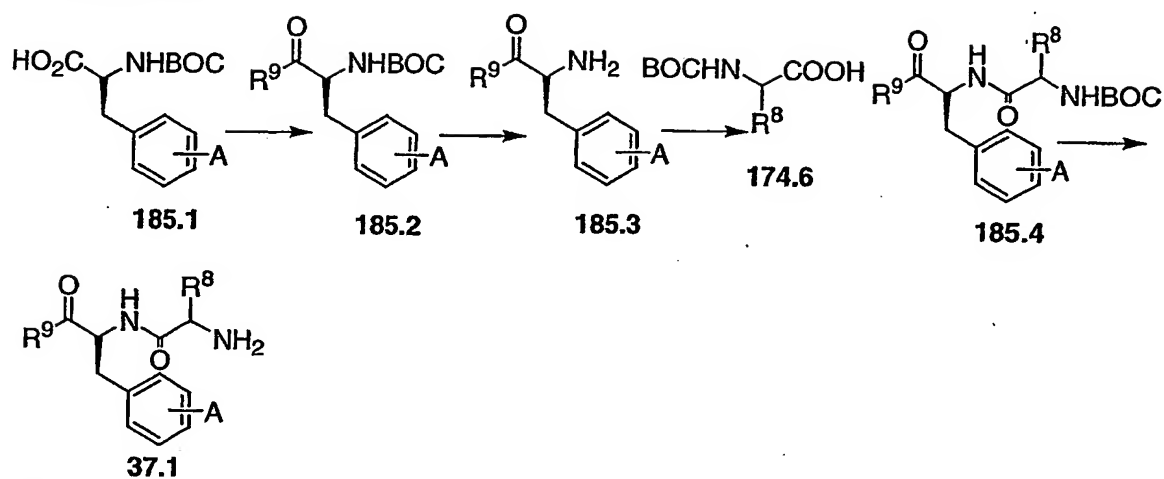


Example 2

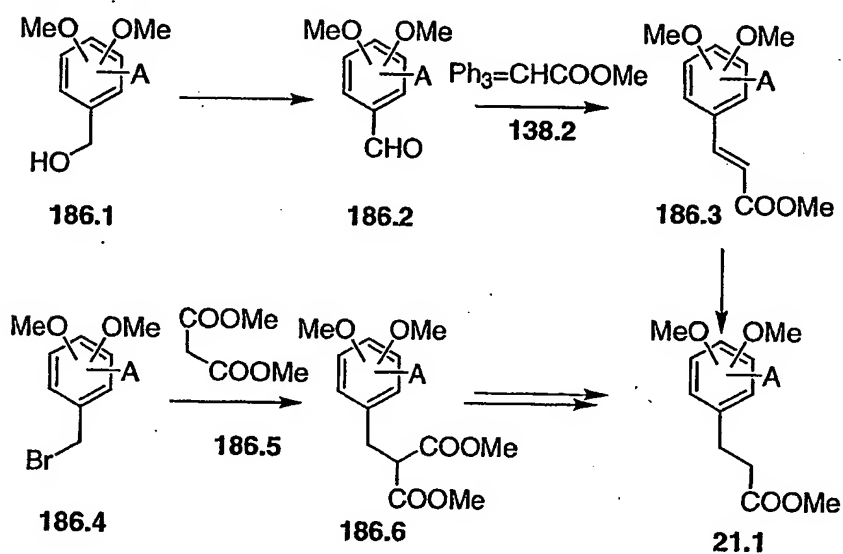


Example 3**Scheme 183****Method****Example****Scheme 184****Example**

Scheme 185

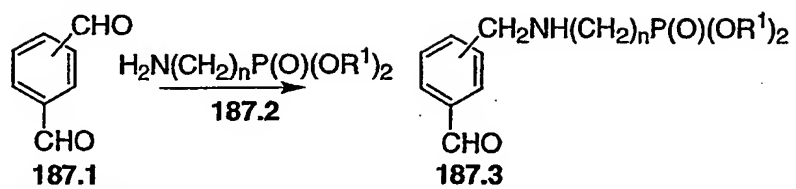


Scheme 186

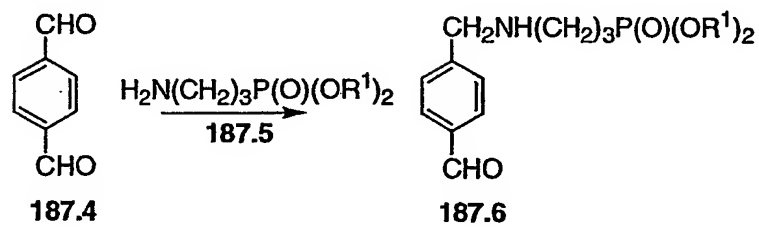


Scheme 187

Method

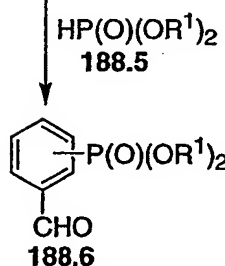
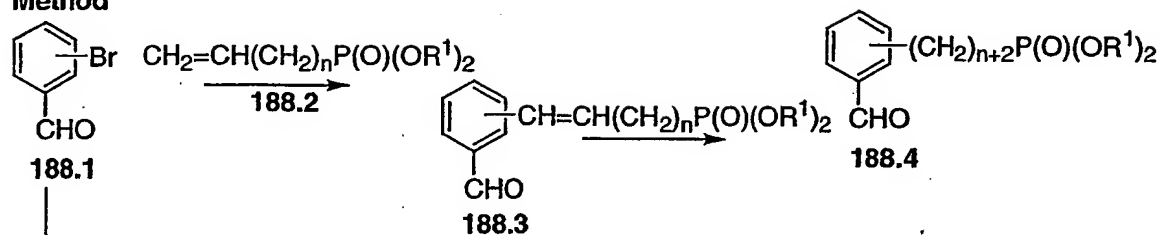


Example

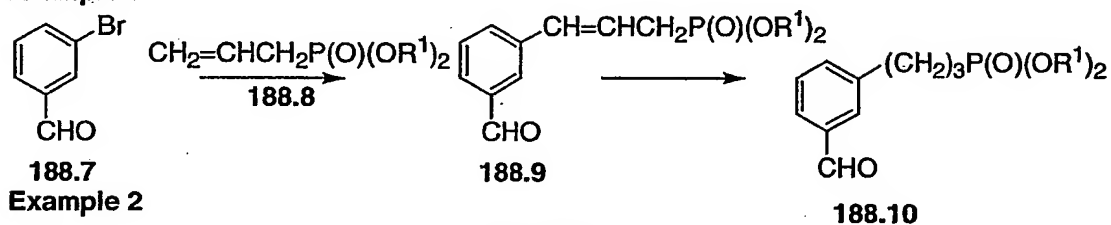


Scheme 188

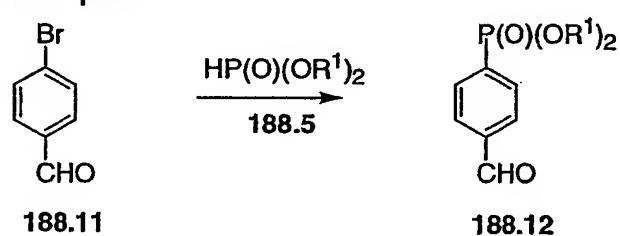
Method



Example 1

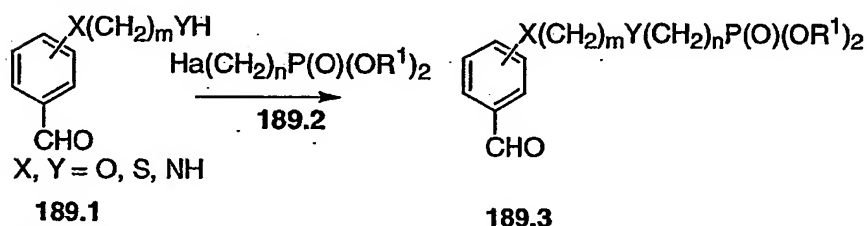


Example 2

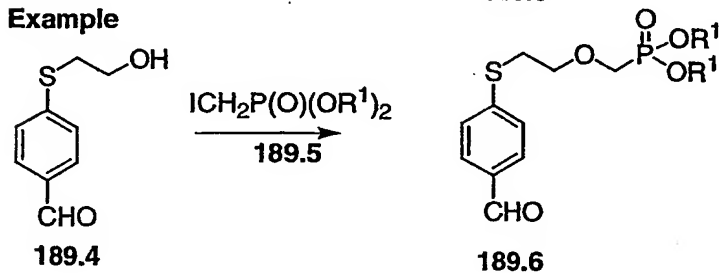


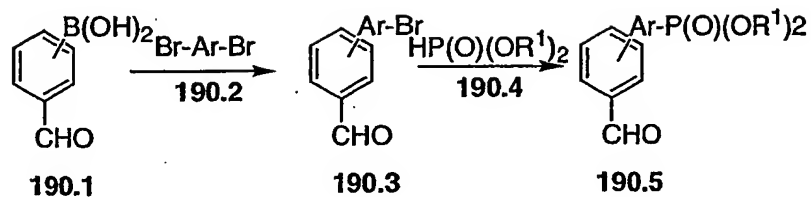
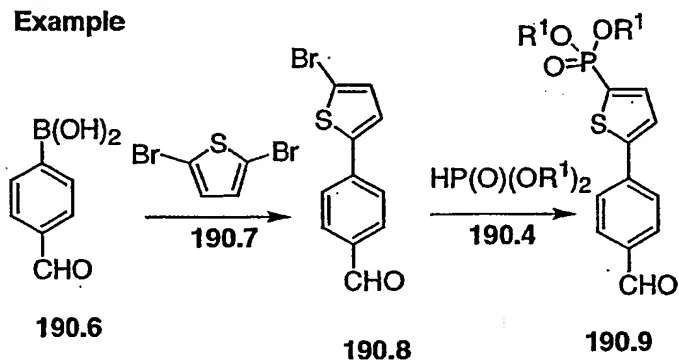
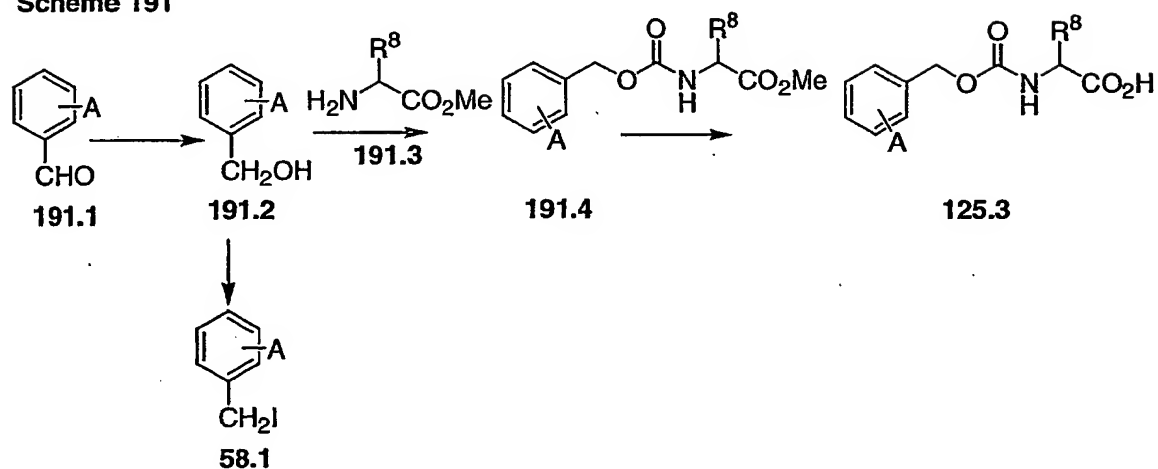
Scheme 189

Method



Example



Scheme 190**Method****Example****Scheme 191****5 Preparation of phosphonate-substituted decahydroquinolines 17.1.**

Schemes 192 – 97 illustrate the preparation of decahydroisoquinoline derivatives 17.1 in which the substituent A is either the group link P(O)(OR¹)₂ or a precursor, such as [OH], [SH], Br.

The compounds are employed in the preparation of the intermediate phosphonate esters 5, 12 and 21.

Scheme 192 illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the benzenoid intermediate 192.4 are shown.

In the first route, 2-hydroxy-6-methylphenylalanine 192.1, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative 192.2. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product 192.2, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product 192.3. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound 192.3 is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline 192.4, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline 192.4 is obtained from 2-hydroxyphenylalanine 192.5, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem. Rev., 1995, 95, 1797.

Typically, the substrate 192.5 is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product 192.4, in which R is H. Catalytic hydrogenation of the latter compound, using, for example, a platinum catalyst, as described in J. Am. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-substituted decahydroisoquinoline 192.6. The reduction is also performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline 192.4 is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°C, to afford the decahydroisoquinoline 192.6.

Protection of the carboxyl and NH groups present in **192.6**, for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example,
5 pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **192.9**, in which R is trichloroethyl and R¹ is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Am. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butoxy aluminum hydride, as described in J. Am. Chem. Soc., 80, 5372, 1958, then affords the alcohol
10 **192.10**.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as isopropanol, at ambient temperature, to afford the alcohol **192.10**.

The alcohol **192.6** is converted into the thiol **192.13** and the amine **192.14**, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry.

15 For example, the alcohol **192.6** is converted into an activated ester such as the trifluoromethanesulfonyloxy ester or the methanesulfonate ester **192.7**, by treatment with methanesulfonyl chloride and a base. The mesylate **192.7** is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement
20 of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol **192.13**.

For example, the mesylate **192.7** is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **192.12**, in which R is COCH₃. The product then treated with a mild
25 base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol **192.13**.

The mesylate **192.7** is treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p. 399, followed by deprotection as described previously, to afford the amine
30 **192.14**.

For example, the mesylate **192.7** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such

as, for example, dimethylformamide, at ambient temperature, to afford the displacement product 192.8, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine 192.14.

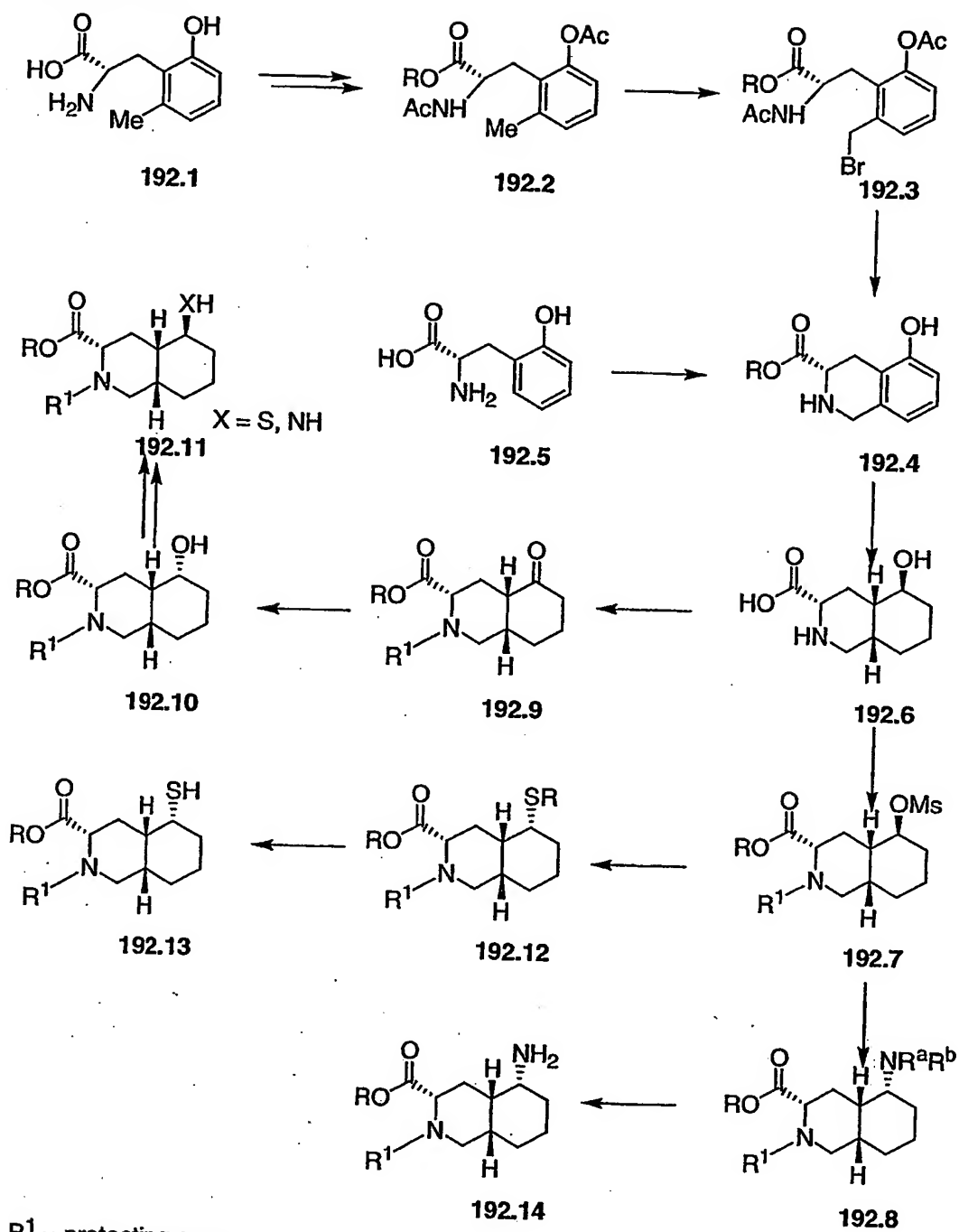
- 5 The application of the procedures described above for the conversion of the β -carbinol 192.6 to the α -thiol 192.13 and the α -amine 192.14 can also be applied to the α -carbinol 192.10, so as to afford the β -thiol and β -amine, 192.11.

- Scheme 193 illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain.
- 10 In this procedure, an alcohol, thiol or amine 193.1 is reacted with a bromoalkyl phosphonate 193.2, under the conditions described above for the preparation of the phosphonate 155.4 (Scheme 155), to afford the displacement product 193.3. Removal of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described
- 15 below, (Scheme 197) then yields the amine 193.4.

- For example, the thiol 193.5, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, 193.6, the preparation of which is described in J.
- 20 Am. Chem. Soc., 2000, 122, 1554 to afford the displacement product 193.7. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme 197) then yields the amine 193.8.

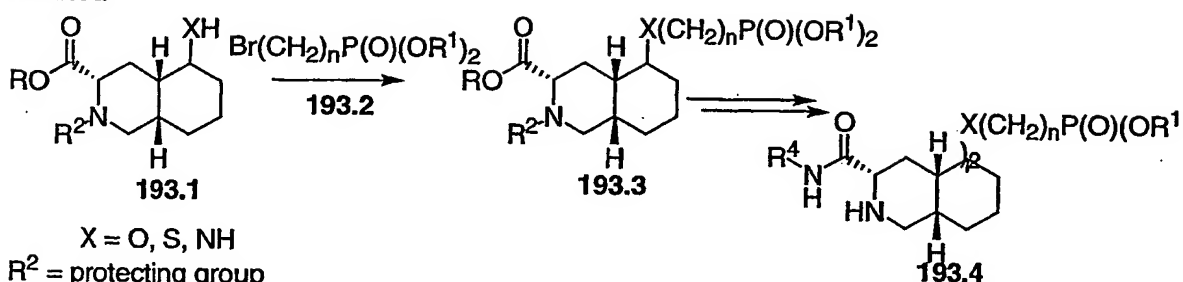
- Using the above procedures, but employing, in place of the α -thiol 193.5, the alcohols, thiols or amines 192.6, 192.10, 192.11, 192.13, 192.14, of either α - or β -orientation, there are
- 25 obtained the corresponding products 193.4, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme 192

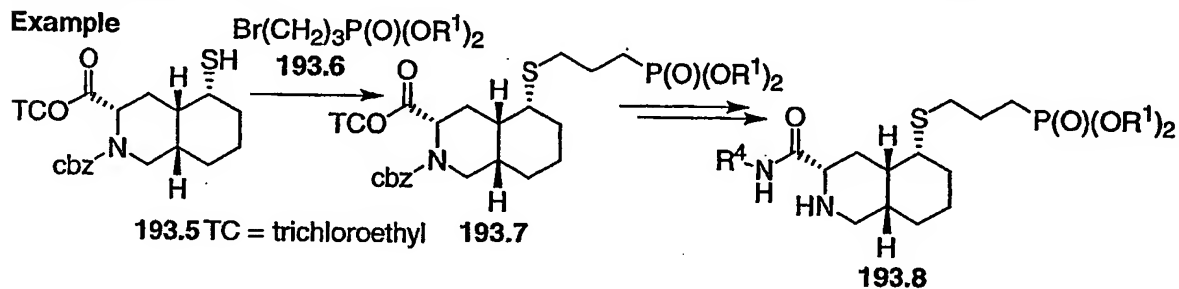


Scheme 193

Method

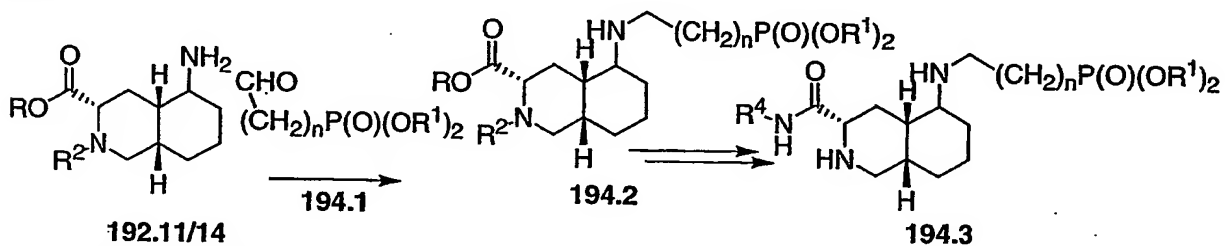


Example

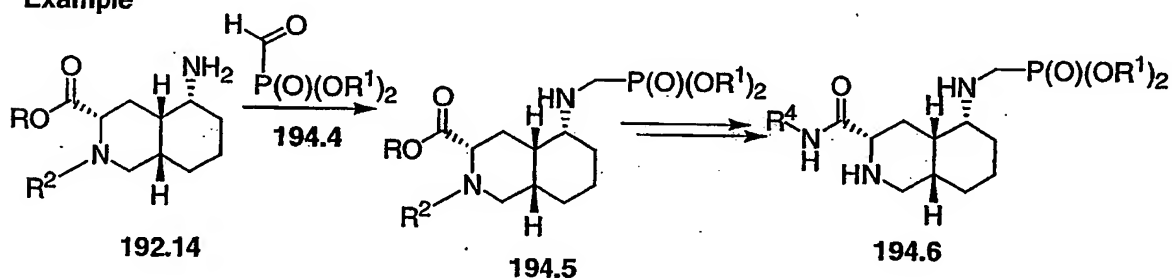


Scheme 194

Method



Example



Scheme 194 illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p. 421.

In this procedure, the amines **192.14** or **192.11** are reacted with a phosphonate aldehyde **194.1**, in the presence of a reducing agent, to afford the alkylated amine **194.2**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **197**) then yields the amine **194.3**.

- 5 For example, the protected amino compound **192.14** is reacted with a dialkyl formylphosphonate **194.4**, the preparation of which is described in U.S. Patent 3,784,590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **194.5**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **194.6**.
- 10 Using the above procedures, but employing, instead of the α -amine **192.14**, the β isomer, **192.11** and/or different aldehydes **194.1**, there are obtained the corresponding products **194.3**, in which the orientation of the side chain is the same as that of the amine precursor.

- 15 Scheme **195** depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.
- In this procedure, a dialkyl mercaptoalkyl phosphonate **195.2** is reacted with a mesylate **195.1**, to effect displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product **195.3**. Deprotection of the ester group, followed by conversion of the acid
- 20 to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **195.4**.

- For example, the protected mesylate **195.5** is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate **195.6**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the
- 25 presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thioether phosphonate **195.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **195.8**

- Using the above procedures, but employing, instead of the phosphonate **195.6**, different
- 30 phosphonates **195.2**, there are obtained the corresponding products **195.4**.

Scheme 196 illustrates the preparation of decahydroisoquinoline phosphonates 196.4 in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates 196.1 and a bromomethyl-substituted arylphosphonate 196.2. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant 196.1. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate is employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is employed. The displacement reaction affords the ether, thioether or amine compounds 196.3. Deprotection of the ester group, followed by conversion of the acid to the R⁴NH amide and N-deprotection, as described in Scheme 197, then yields the amine 196.4.

For example, the alcohol 196.5 is reacted at ambient temperature with a dialkyl 3-bromomethyl benzylphosphonate 196.6, the preparation of which is described above, (Scheme 143). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a strong base, such as, for example, lithium hexamethyldisilylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate 196.6, to afford the product 196.7. Deprotection of the ester group, followed by conversion of the acid to the R⁴NH amide and N-deprotection, as described in Scheme 197, then yields the amine 196.8.

Using the above procedures, but employing, instead of the β -carbinol 196.5, different carbinols, thiols or amines 196.1, of either α - or β -orientation, and/or different phosphonates 196.2, in place of the phosphonate 196.6, there are obtained the corresponding products 196.4 in which the orientation of the side-chain is the same as that of the starting material 196.1.

Schemes 193 - 196 illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme 197 illustrates the conversion of the latter group of compounds 197.1 (in which the group A is link-P(O)(OR¹)₂ or optionally protected precursor substituents, such as, for example, OH, SH, or NH₂ to the corresponding R⁴NH amides 17.1.

As shown in Scheme 197, the ester compounds 197.1 are deprotected to form the corresponding carboxylic acids 197.2. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R², and

the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is removed by treatment with zinc in acetic acid, as described in J. Am. Chem. Soc., 88, 852, 1966. Conversion of the carboxylic acid **197.2** to the R⁴NH amide **197.4** is then accomplished by reaction, as described in Scheme 1, of the carboxylic acid, or an activated derivative thereof, with the amine R⁴NH₂ (**197.3**) to afford the amide **197.4**. Deprotection of the NR² group, as described above, then affords the free amine **17.1**.

Preparation of carbamates.

- 10 The phosphonate esters **13 - 20** in which the R¹⁰ is alkoxy, and the phosphonate esters **22** contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.
- 15 Scheme **198** illustrates various methods by which the carbamate linkage is synthesized. As shown in Scheme **198**, in the general reaction generating carbamates, a carbinol **198.1**, is converted into the activated derivative **198.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **198.2** is then reacted with an amine **198.3**, to afford the carbamate product **198.4**. Examples **1 - 7** in
- 20 Scheme **198** depict methods by which the general reaction is effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.
- Scheme **198**, Example **1** illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **198.1**. In this procedure, the carbinol is reacted with phosgene, in an inert solvent such as toluene, at about 0°C, as described in Org. Syn. Coll. Vol. 3, 167, 1965,
- 25 or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **198.6**. The latter compound is then reacted with the amine component **198.3**, in the presence of an organic or inorganic base, to afford the carbamate **198.7**. For example, the chloroformyl compound **198.6** is reacted with the amine **198.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of
- 30 aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **198.7**. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 198, Example 2 depicts the reaction of the chloroformate compound 198.6 with imidazole to produce the imidazolide 198.8. The imidazolide product is then reacted with the amine 198.3 to yield the carbamate 198.7. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°C, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 198 Example 3, depicts the reaction of the chloroformate 198.6 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 198.10. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 198.19 - 198.24 shown in Scheme 198, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 198.19, N-hydroxysuccinimide 198.20, or pentachlorophenol, 198.21, the mixed carbonate 198.10 is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 198.22 or 2-hydroxypyridine 198.23 is performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme 198 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 198.8 is employed. In this procedure, a carbinol 198.5 is reacted with an equimolar amount of carbonyl diimidazole 198.11 to prepare the intermediate 198.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 198.8 is then reacted with an equimolar amount of the amine RNH₂ to afford the carbamate 198.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 198.7.

Scheme 198, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxy carbonylbenztriazole 198.13. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride 198.12, to afford the alkoxy carbonyl product 198.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. The product is then reacted with the amine RNH₂ to afford the

carbamate **198.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80°C as described in Syn., 1977, 704.

Scheme **198**, Example **6** illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, **198.14**, is reacted with a carbinol **198.5** to afford the intermediate

5 alkyloxycarbonyl intermediate **198.15**. The latter reagent is then reacted with the amine R'NH₂ to afford the carbamate **198.7**. The procedure in which the reagent **198.15** is derived from hydroxybenztriazole **198.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **198.15** is derived from N-hydroxysuccinimide **198.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **198.15** is derived from 2-hydroxypyridine
10 **198.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **198.15** is derived from 4-nitrophenol **198.24** is described in Syn. 1993, 199. The reaction between equimolar amounts of the carbinol ROH and the carbonate **198.14** is conducted in an inert organic solvent at ambient temperature.

Scheme **198**, Example **7** illustrates the preparation of carbamates from alkoxy carbonyl azides
15 **198.16**. In this procedure, an alkyl chloroformate **198.6** is reacted with an azide, for example sodium azide, to afford the alkoxy carbonyl azide **198.16**. The latter compound is then reacted with an equimolar amount of the amine R'NH₂ to afford the carbamate **198.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

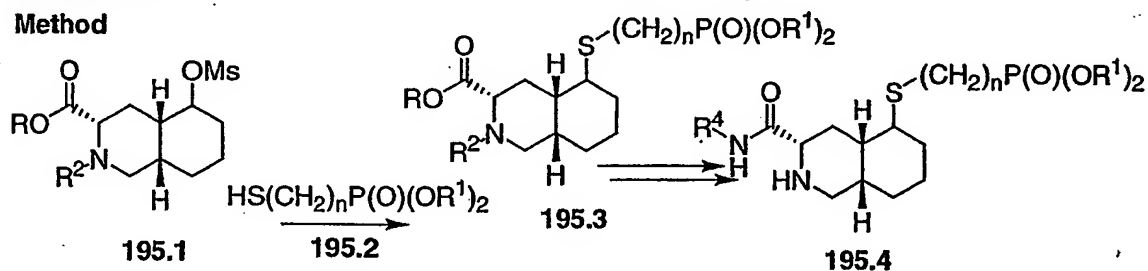
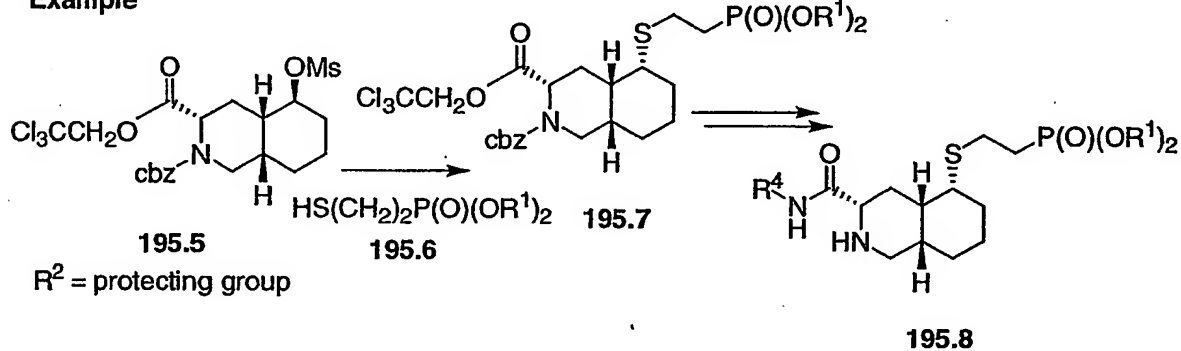
20 Scheme **198**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine **198.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate
25 **198.7**.

Scheme **198**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **198.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane
30 and the like, to afford the carbamate **198.7**.

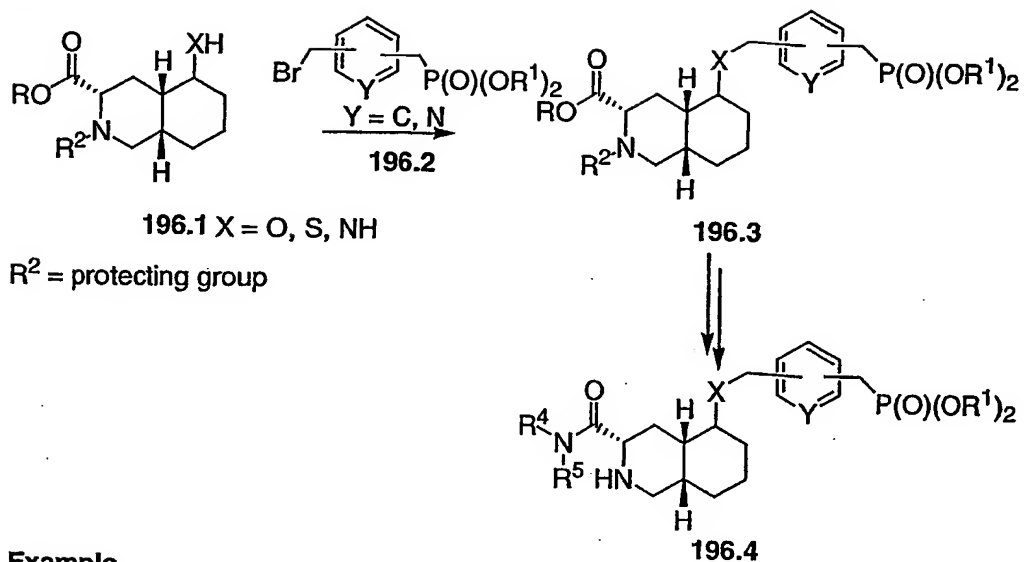
Scheme **198**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine R'NH₂. In this procedure, which is described in Chem.

Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **198.7**.

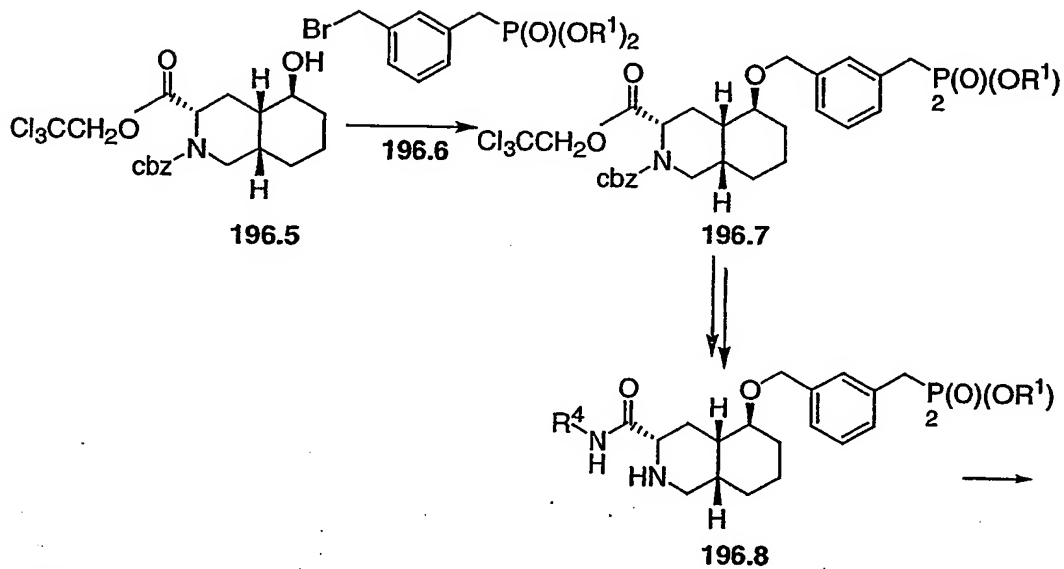
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Scheme 195**Method****Example**

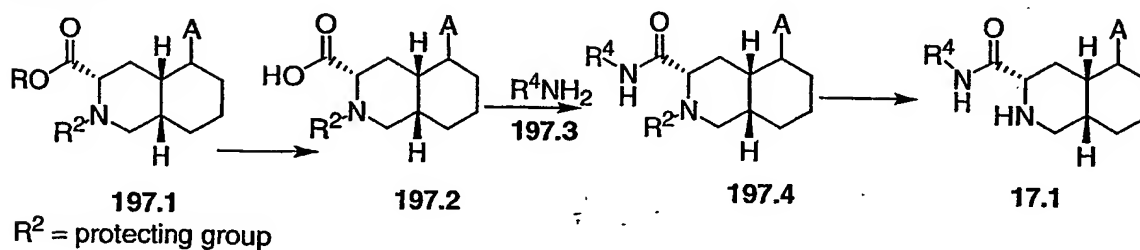
Scheme 196
Method



Example

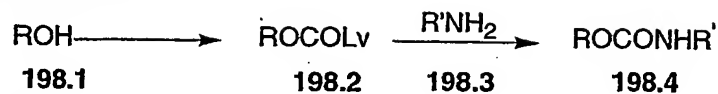


Scheme 197
Method

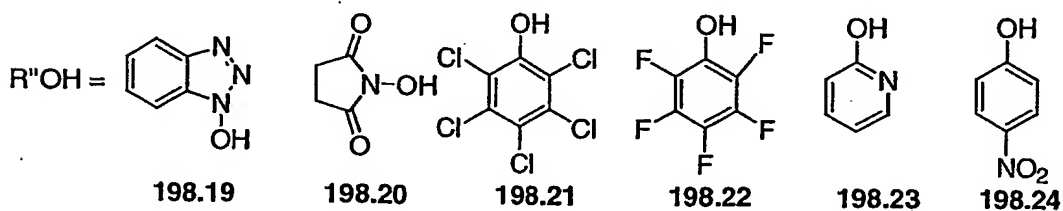
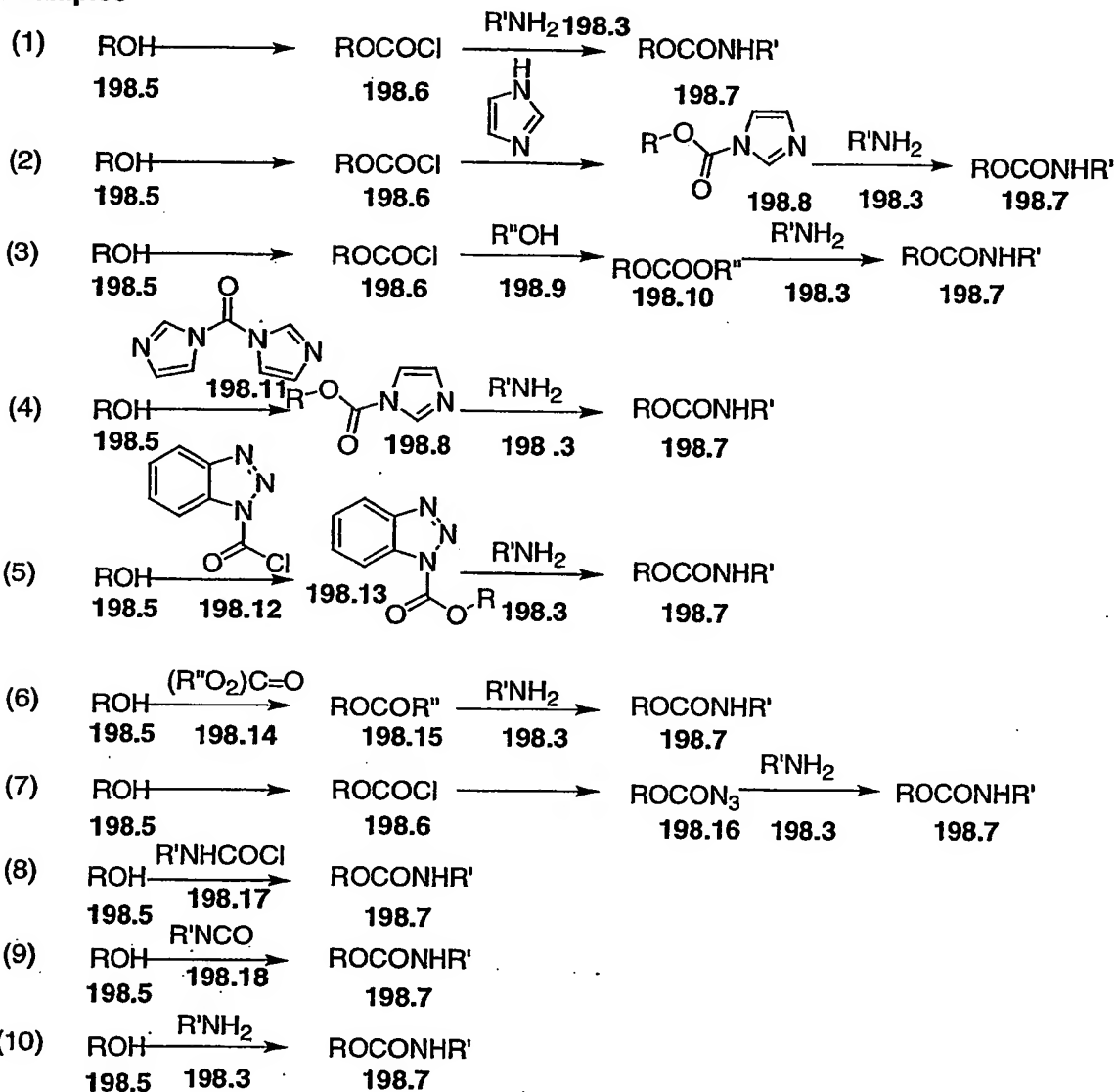


Scheme 198

General reaction



Examples



Interconversions of the phosphonates R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

Schemes 1 - 197 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may be the same or different. The R¹ groups attached to the phosphonate esters 1 - 24, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 199. The group R in Scheme 199 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1 - 24 or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1 - 24. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 199.1 into the corresponding phosphonate monoester 199.2 (Scheme 199, Reaction 1) is accomplished by a number of methods. For example, the ester 199.1 in which R¹ is an aralkyl group such as benzyl, is converted into the monoester compound 199.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester 199.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 199.2 is effected by treatment of the ester 199.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters 199.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, are converted into the monoesters 199.2 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, are converted into the monoester 199.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **199.1** or a phosphonate monoester **199.2** into the corresponding phosphonic acid **199.3** (Scheme 199, Reactions 2 and 3) is effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **199.2** in which R¹ is aralkyl such as benzyl, is converted into the corresponding phosphonic acid **199.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **199.2** in which R¹ is alkenyl such as, for example, allyl, is converted into the phosphonic acid **199.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **199.1** in which R¹ is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **199.1** in which R¹ is phenyl is described in J. Am. Chem. Soc., 78, 2336, 1956.

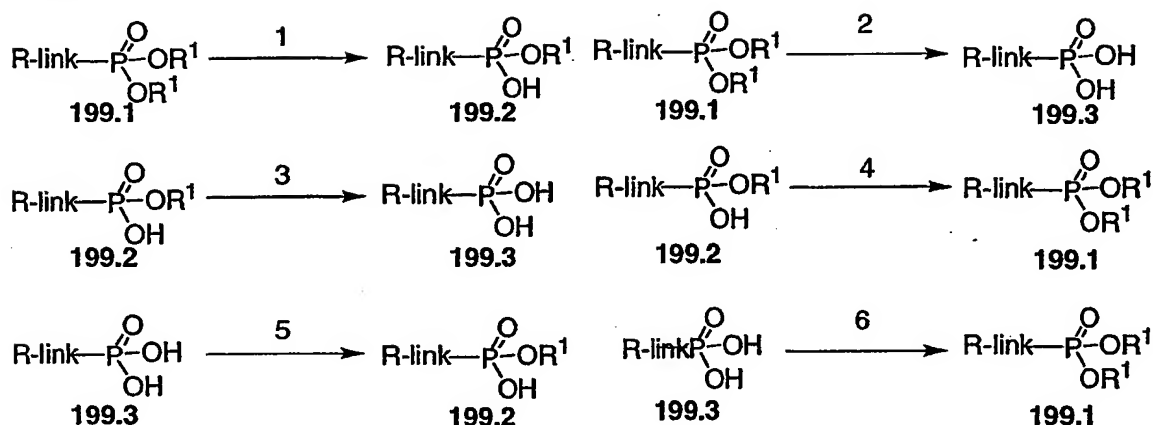
The conversion of a phosphonate monoester **199.2** into a phosphonate diester **199.1** (Scheme 199, Reaction 4) in which the newly introduced R¹ group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl is effected by a number of reactions in which the substrate **199.2** is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **199.2** to the diester **199.1** is effected by the use of the Mitsunobu reaction, as described above (Scheme 142). The substrate is reacted with the hydroxy compound R¹OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **199.2** is transformed into the phosphonate diester **199.1**, in which the

introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br , in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester is transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **199.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester **199.1**.

A phosphonic acid $R\text{-link-P}(O)(OH)_2$ is transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme 199, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $R\text{-link-P}(O)(OR^1)_2$ **199.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid $R\text{-link-P}(O)(OH)_2$ **199.3** is transformed into a phosphonate diester $R\text{-link-P}(O)(OR^1)_2$ **199.1** (Scheme 199, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **199.3** are transformed into phosphonic esters **199.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca $70^\circ C$. Alternatively, phosphonic acids **199.3** are transformed into phosphonic esters **199.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **199.1**.

Scheme 199



General applicability of methods for introduction of phosphonate substituents.

- The procedures described for the introduction of phosphonate moieties (Schemes 133 - 192) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into indanols (Schemes 133 - 137) are applicable to the introduction of phosphonate moieties into phenylpropionic acids, thiophenols, tert. butylamines, pyridines, benzyl halides, ethanolamines, aminochromans, phenylalanines and benzyl alcohols, and the methods described for the introduction of phosphonate moieties into the above-named substrates (Schemes 138 - 192) are applicable to the introduction of phosphonate moieties into indanol substrates.

- Preparation of phosphonate intermediates 23 and 24 with phosphonate moieties incorporated into the R^2 , R^3 , R^5 , R^{10} or R^{11} groups.**

- The chemical transformations described in Schemes 1 - 192 illustrate the preparation of compounds 1 - 22 in which the phosphonate ester moiety is attached to the indanol moiety, (Schemes 1 - 4, 76 - 84), the phenyl group (Schemes 5 - 8, 21 - 24, 37 - 40, 49 - 52, 58 - 61, 67 - 68, 74, 75, 101 - 108, 125 - 132) the tert. butylamine group, (Schemes 9 - 12, 25 - 28, 41 - 44, 109 - 116), the pyridine group (Schemes 13 - 16), the decahydroisoquinoline group (Schemes 17 - 20, 45 - 48, 117 - 124), the ethanolamine group (Schemes 29 - 32, 93 - 100), the aminochroman group (Schemes 33 - 36, 85 - 92), and the thiophenyl group

(Schemes 53 – 57, 62 – 66, 69 – 73). The various chemical methods employed for the introduction of phosphonate ester groups into the above-named moieties can, with appropriate modifications known to those skilled in the art, be applied to the introduction of a phosphonate ester group into the compounds R^2R^3NH , R^5SH , R^5CH_2I , $R^{10}CO$, $R^{11}SH$, and $R^{11}CH_2CH(NH_2)COOH$. The resultant phosphonate-containing analogs, designated as $R^{2a}R^{3a}NH$, $R^{5a}SH$, $R^{5a}CH_2I$, $R^{10a}CO$, $R^{11a}SH$, and $R^{11a}CH_2CH(NH_2)COOH$ are then, using the procedures described above, employed in the preparation of the compounds 23 and 24. The procedures required for the utilization of the phosphonate-containing analogs are the same as those described above for the utilization of the compounds R^2R^3NH , R^5SH , R^5CH_2I , $R^{10}CO$, $R^{11}SH$, and $R^{11}CH_2CH(NH_2)COOH$.

For example, Schemes 200-204 and Schemes 205-207 depict the introduction of the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as, $[OH]$, $[NH_2]$, $[SH]$ onto the R^2R^3NH amines A10a and A10b in Chart 4, to give amines 200.5 and 205.10 respectively. These amine products are then utilized in the generation of compounds 23 where R^2R^3NH is now $R^{2a}R^{3a}NH$ in Chart 3 following the same procedures outlined in Schemes 13 and 15 but replacing the amine 13.1 with 200.5 or 205.10 respectively.

Preparation of piperazine furan compounds 200.5 with phosphonate attachments

Schemes 200 - 204 depict the preparation of the piperazine furan aryl phosphonate compounds 200.5 that are employed in the preparation of the phosphonate esters 23 where R^2R^3NH is now $R^{2a}R^{3a}NH$ as described above.

Scheme 200 depicts the preparation of piperazine biaryl phosphonates in which the terminal aryl ring bears the phosphonate moiety through a linking group. Methods for the preparation of the reagents 200.2 are shown in Schemes 201-204. Furan 200.1 prepared as described in WO02/096359, is treated with the aryl bromide 200.2 in the presence of palladium catalyst by the method of Gronowitz et al. (J. Heterocyclic Chemistry, 1995, 35, p. 771) to give 200.3. The product 200.3 is then subjected to the sequence of reactions and conditions described in WO02/096359 to prepare the piperazine 200.5. The preparation of reagent 200.6 where $R^4 = CH_2CF_3$ is also described in WO02/096359. Alternatively, deprotection of amines 164.1 by treatment with trifluoroacetic acid at room temperature as described in Int. J. Pept. Protein Res., 12, 258, 1978, followed by treatment with alloc chloro formate and a base such as

pyridine, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Third Edition 1999 p. 526-527 yields **200.6** where R⁴ is as defined in Chart 1.

Scheme **201** depicts the preparation of phosphonates **200.2** in which the phosphonate moiety is attached to the phenyl ring by means of a heteroatom and an alkyl chain. Many halogenated aromatic compounds are commercially available or can be generated from readily available aromatic compounds through aromatic substitution. Methods for chlorinating or brominating an aryl ring can be found in Comprehensive Organic Transformations, by R. C. Larock, 2nd Edition, 1999 p619. The phenol, thiol or amine **201.1** is reacted with a derivative of a hydroxymethyl dialkylphosphonate **140.2**, in which Lv is a leaving group such as methanesulfonyloxy and the like. The reaction is conducted in a polar aprotic solvent, in the presence of an organic or inorganic base, to afford the displacement product **201.2**. For example, the phenols **201.5** (Aldrich) or **201.9** (Apollo-Chem) are reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **140.6**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether products. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C, to afford the products **201.6** and **201.10** respectively. Alternatively treatment of amine **201.11** (Apollo) or **201.7** (Aldrich) with the dialkyl trifluoromethylsulfonyloxymethyl phosphonate **140.6** in the presence of a base as described above affords **201.12** and **201.8** respectively.

Using the above procedures, but employing, in place of the phenols and amines, different phenols, thiols or amines **201.1**, and /or different dialkyl trifluoromethyl-sulfonyloxymethyl phosphonates **140.2**, the corresponding products **201.2** are obtained.

Scheme **202** illustrates the preparation of compounds in which the phosphonate group is attached by means of an aminoalkyl chain. In this procedure, the aldehyde **202.1** is reacted, under reductive amination conditions, as described in Scheme 135, with a dialkyl aminoalkyl phosphonate **202.2**, to give the amine **202.3**.

For example, the aldehyde **202.4** (Aldrich) is reacted in ethanol with a dialkyl aminoethyl phosphonate **166.5**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, and sodium triacetoxyborohydride, to produce the amine **202.5**.

Using the above procedures, but employing, in place of the aldehyde, 202.4 different aldehydes 202.1 and different phosphonates 202.2, the corresponding products 202.3 are obtained.

5 Scheme 203 illustrates the preparation of aryl halides incorporating phosphonate groups attached by means of an amide group. In this procedure, a carboxy-substituted aryl halide 203.1 is coupled, as described in Scheme 1, with a dialkyl aminoalkyl phosphonate 202.2 to prepare the amide 203.2.

For example, 2-chloro-4-bromobenzoic acid 203.4, the preparation of which is described in
10 Bioorg. Med. Chem. Lett. 2001, 11, 10, p. 1257, is coupled in dimethylformamide solution, in the presence of dicyclohexylcarbodiimide, with a dialkyl aminoethyl phosphonate 166.5, the preparation of which is described in J. Org. Chem., 2000, 65, 676, to afford the amide 203.5. Using the above procedures, but employing, in place of the benzoic acid 203.4, different benzoic acids 203.1, and/or different aminoalkyl phosphonates 202.2, the corresponding
15 products 203.2 are obtained.

Scheme 204 illustrates the preparation of phosphonate-substituted aryl halides in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a benzoic acid 203.1 is first methylated to give methyl ester 204.1 and then reduced with a reducing
20 agent, as described in J. Org. Chem. 1987, 52, p. 5419 to give alcohol 204.2. The alcohol 204.2 is then reacted with hexabromoethane in the presence of triphenyl phosphine as described in Syn. 1983, p. 139 to give the bromide 204.3. The bromide 204.3 is reacted with a sodium dialkyl phosphite 204.5 or a trialkyl phosphite, to give the product 204.4

For example, acid 204.6 (Lancaster) is converted to the methyl ester 204.7 by refluxing in
25 methanol and concentrated sulfuric acid and then reduced with lithium aluminum hydride in THF to give 204.8 as described above. The product 204.8 is reacted with hexabromoethane in the presence of triphenyl phosphine as described in Syn. 1983, p. 139 to give the bromide 204.9. This material is reacted with a sodium dialkyl phosphite 204.5, as described in J. Med. Chem., 35, 1371, 1992, to afford the product 204.10. Alternatively, the bromomethyl
30 compound 204.9 is converted into the phosphonate 204.10 by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure,

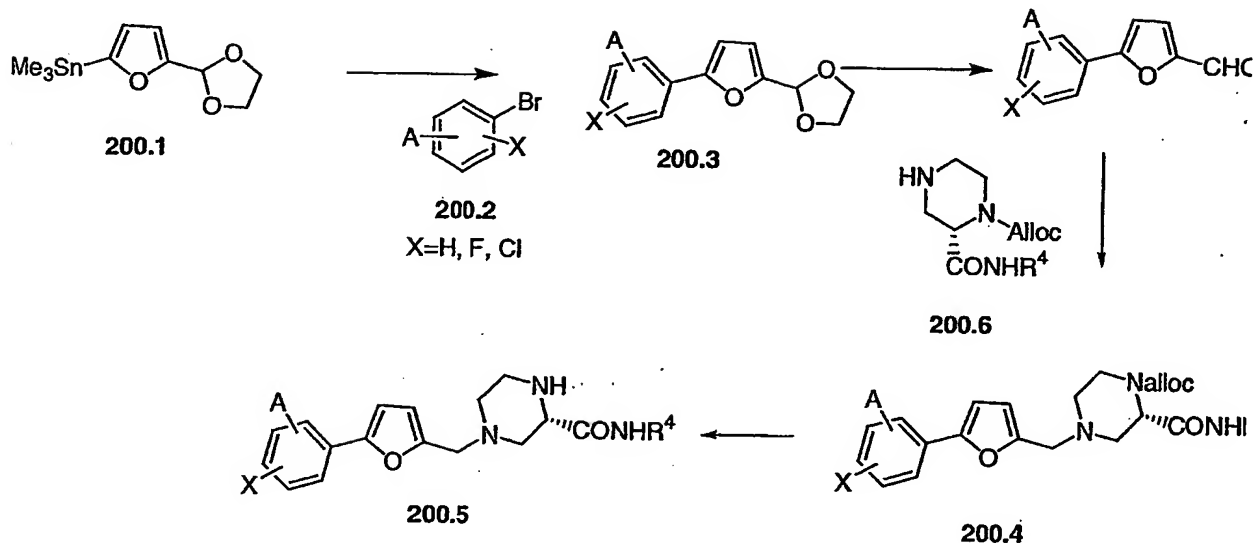
the bromomethyl compound **204.9** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100°C to produce the phosphonate **204.10**.

Using the above procedures, but employing, in place of the acid **204.6**, different acids **203.1**, and different phosphites **204.5** there are obtained the corresponding aryl halides **204.4**.

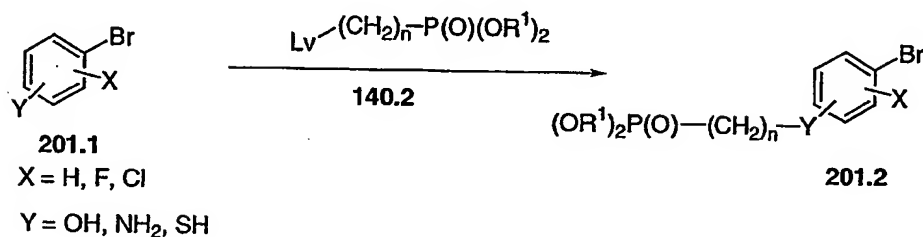
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The phosphonate-containing bromobenzene derivatives prepared as described in Schemes **201** - **204** are then transformed, as described in Scheme **200**, into the phenylfuran piperazine derivatives **200.5**.

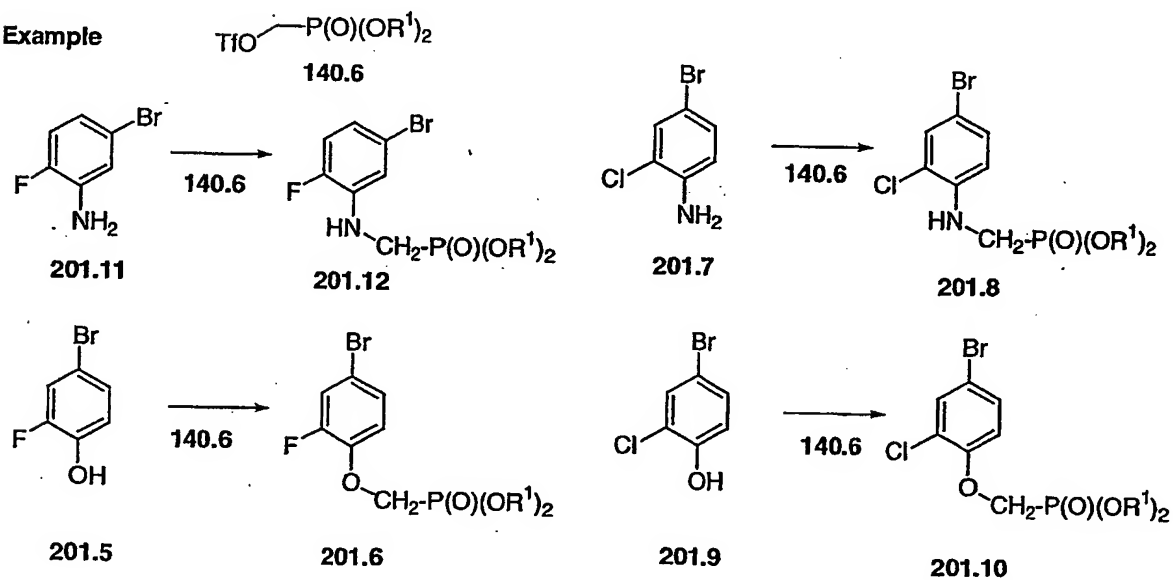
Scheme 200



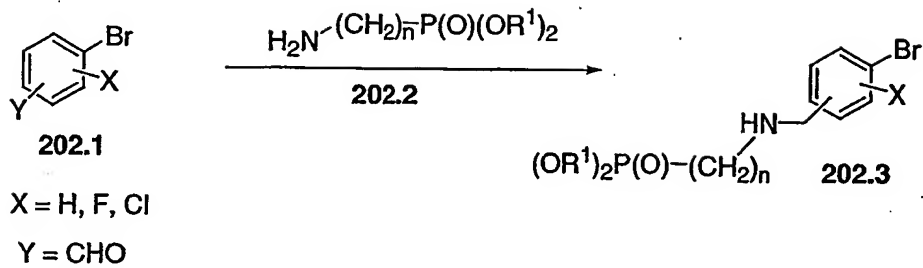
Scheme 201



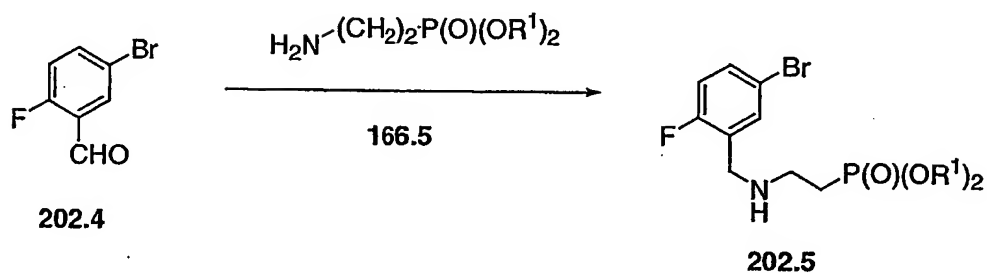
Example



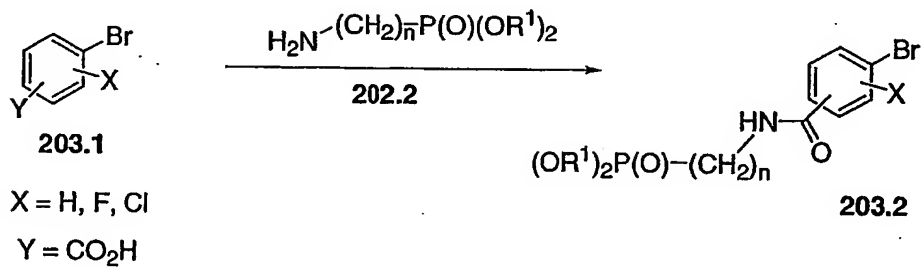
Scheme 202



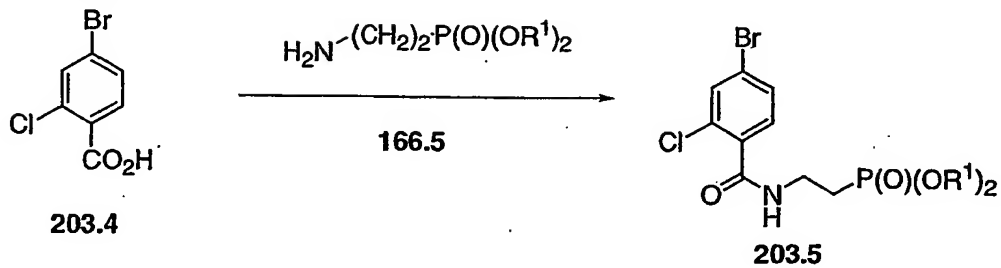
Example



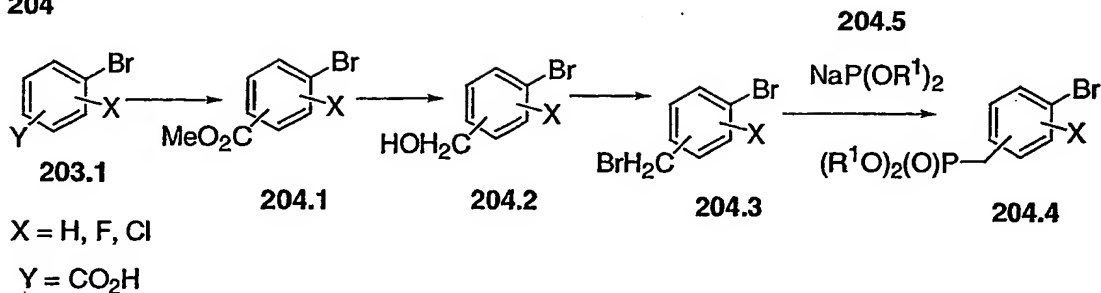
Scheme 203



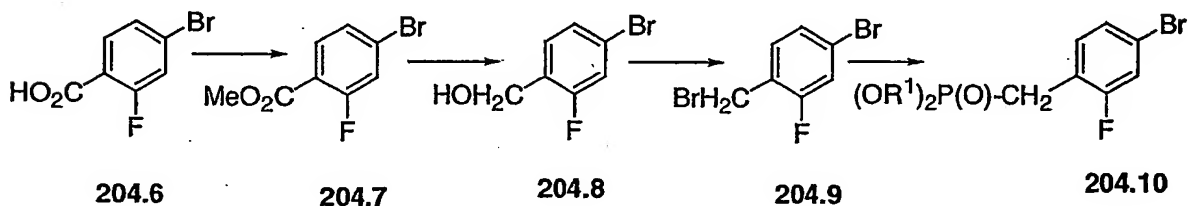
Example



**Scheme
204**



Example



Preparation of piperazine oxazole compounds 205.10 bearing phosphonate attachments

- 5 Schemes 205 - 207 depict the preparation of the piperazine oxazole phosphonate compounds 205.10 that are employed in the preparation of the phosphonate esters 23 where $\text{R}^2\text{R}^3\text{NH}$ is now $\text{R}^{2a}\text{R}^{3a}\text{NH}$ as described above.

- 10 Scheme 205 depicts the preparation of piperazine oxazole phosphonates 205.10 in which the terminal aryl ring bears the phosphonate moiety. The acid 205.1 is converted to the Weinreb amide, for example, as described in J. Med. Chem., 1994, 37, 2918, and then reacted with a methyl Grignard reagent e.g. MeMgBr . Examples of this procedure are reviewed in Org prep Proc Intl 1993, 25, 15. Ketone 205.3 is then brominated using conditions described in Comprehensive Organic Transformations, by R. C. Larock, 2nd Edition, 1999, p. 710-711.
- 15 For example, treatment of 205.3 with bromine in acetic acid yields 205.4. Conversion of the bromomethyl compound 205.4 into the piperazine derivative 205.10, via the intermediates 205.5 - 205.9, is effected by means of the reactions and procedures described in WO02/096359 for related compounds in which R^4 is CH_2CF_3 and A is H.

Scheme 206 illustrates the preparation of benzoic acid phosphonates in which the phosphonate moiety is attached by means of alkylene chains and a heteroatom O, S or N. In this procedure, a benzoic acid 206.1 is protected with a suitable protecting group (see Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 ch5 and then
5 reacted with a an equimolar amount of a dialkyl phosphonate 206.3, in which Ha is a leaving group e.g. halogen, to afford the alkyl phosphonate product 206.4. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile 206.2. In cases in which Y is O, a strong base such as sodium hydride or lithium hexamethyldisilazide is
10 employed. In cases in which Y is S or N, a base such as cesium carbonate or dimethylaminopyridine is employed. Following this reaction the product 206.4 is hydrolyzed by treatment with base to give the acid 206.5

For example, benzoic acid 206.6, (Aldrich) is reacted with diazomethane in ether at 0°C to give the methyl ester 206.7 or simply refluxed in acidic methanol. The ester in acetonitrile at
15 60°C is treated with one molar equivalent of a dialkyl iodomethyl phosphonate 206.8, (Lancaster) to give the ether product 206.9. This product 206.9 is then hydrolyzed by treatment with lithium hydroxide in aqueous THF to give the acid 206.10.

Using the above procedures, but employing, in place of the benzoic acid 206.6, different acids 206.1, and/or different haloalkyl phosphonates 206.3, the corresponding products 206.5 are
20 obtained.

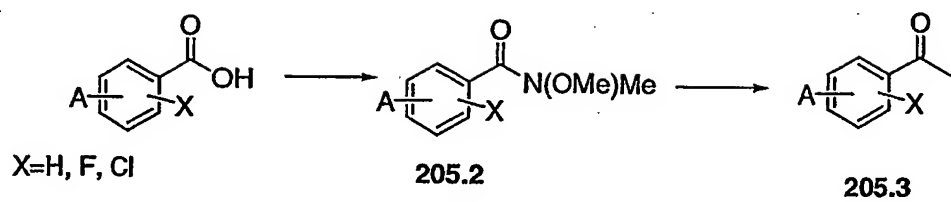
Scheme 207 depicts the preparation of phosphonate esters linked to a benzoic acid nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 207.3 is
25 coupled with an aromatic bromo compound 207.2. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as
30 tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product 207.4. Deprotection, or hydrogenation of the double bond

followed by deprotection, affords respectively the unsaturated phosphonate acid **207.5**, or the saturated analog **207.6** respectively.

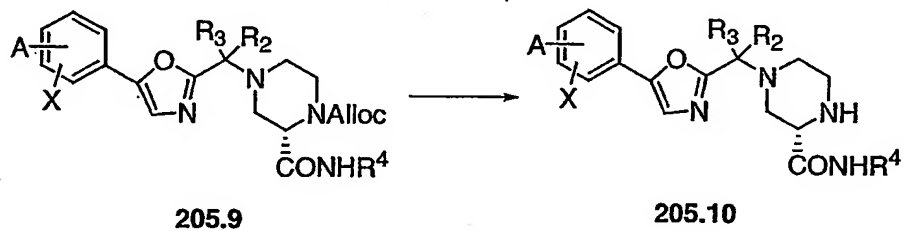
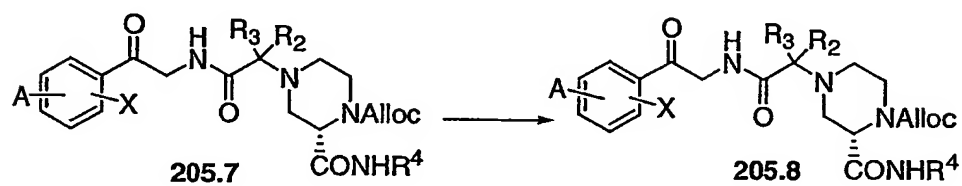
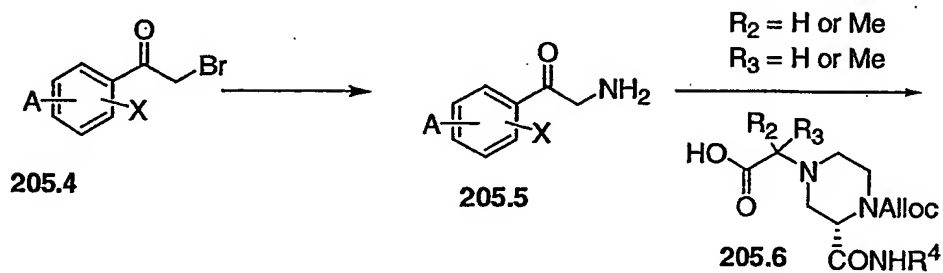
- For example, 4-bromo-3-fluorobenzoic acid **207.7** (Apollo) is converted to the tert butyl ester **207.8** by treatment with t-butanol and DCC in the presence of dimethylaminopyridine. The
- 5 ester **207.8** is then reacted with a dialkyl 1-propenyl phosphonate **150.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the
- 10 coupled product **207.10**. Deprotection as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 406-408, then affords the acid **207.11**. Optionally, the acid **207.11** is subjected to catalytic or chemical reduction, for example using diimide, as described in Scheme 138, to yield the saturated product **207.12**.
- 15 Using the above procedures, but employing, in place of the acid compound **207.7**, different acid compounds **207.1**, and/or different phosphonates **207.3**, there are obtained the corresponding products **207.5** and **207.6**.

- The phosphonate-containing benzoic acids, prepared as described in Schemes 206 and 207,
- 20 are then transformed, using the procedures shown in Scheme 205, into the phenyloxazole piperazine derivatives **205.10**.

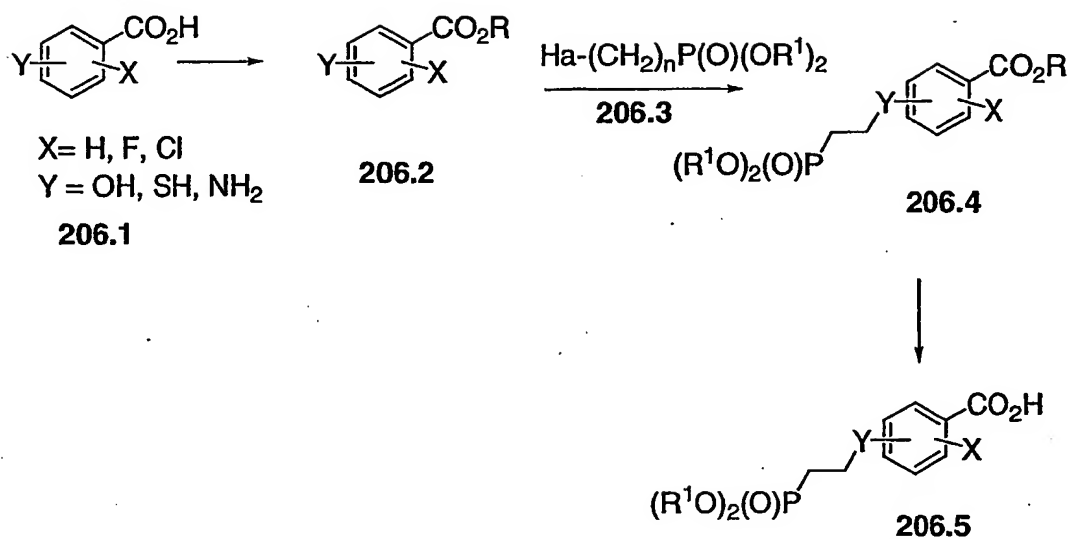
Scheme 205



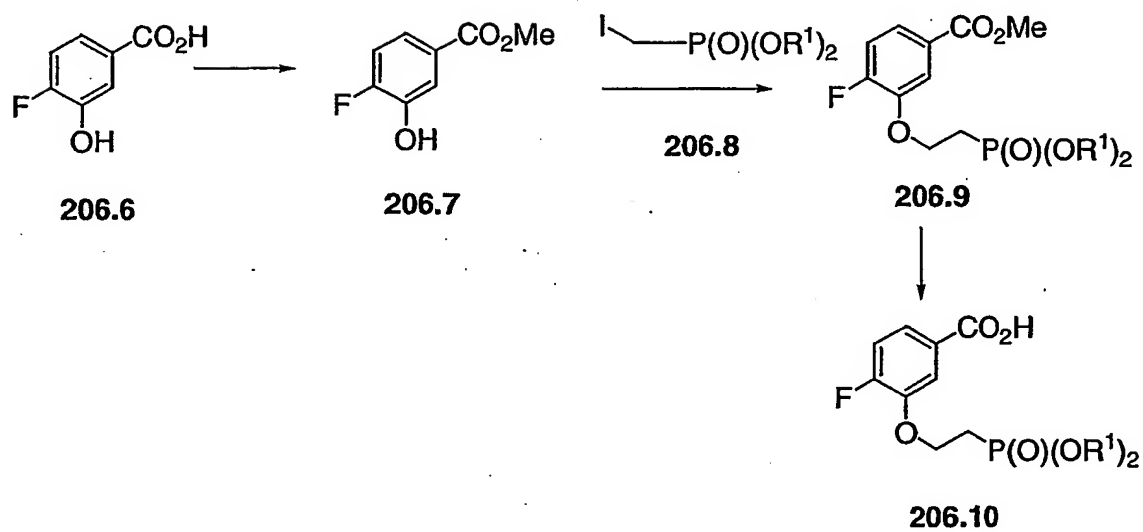
205.1



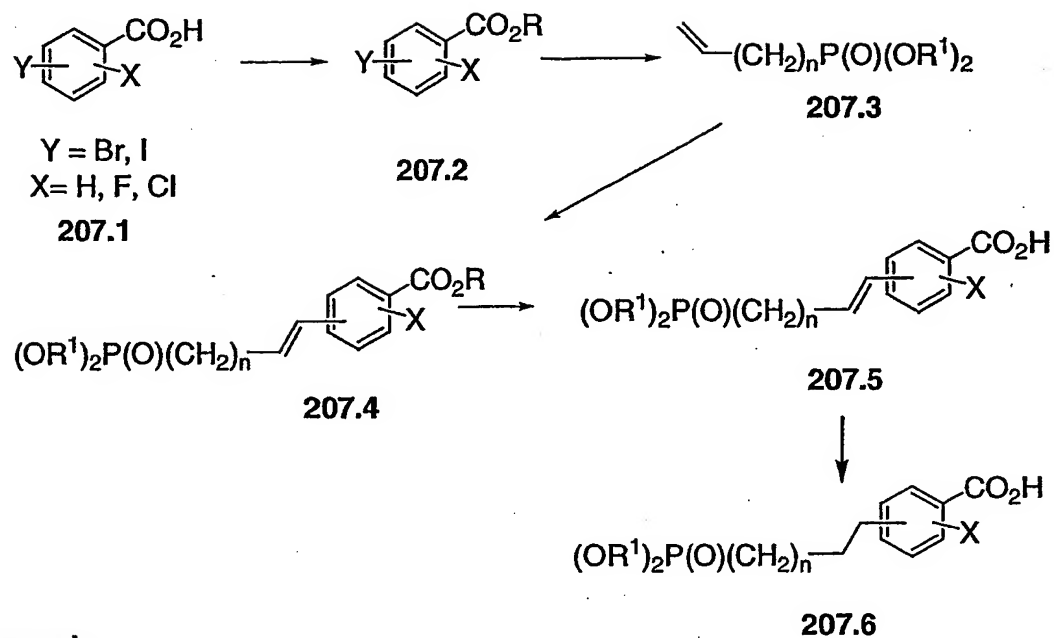
Scheme 206



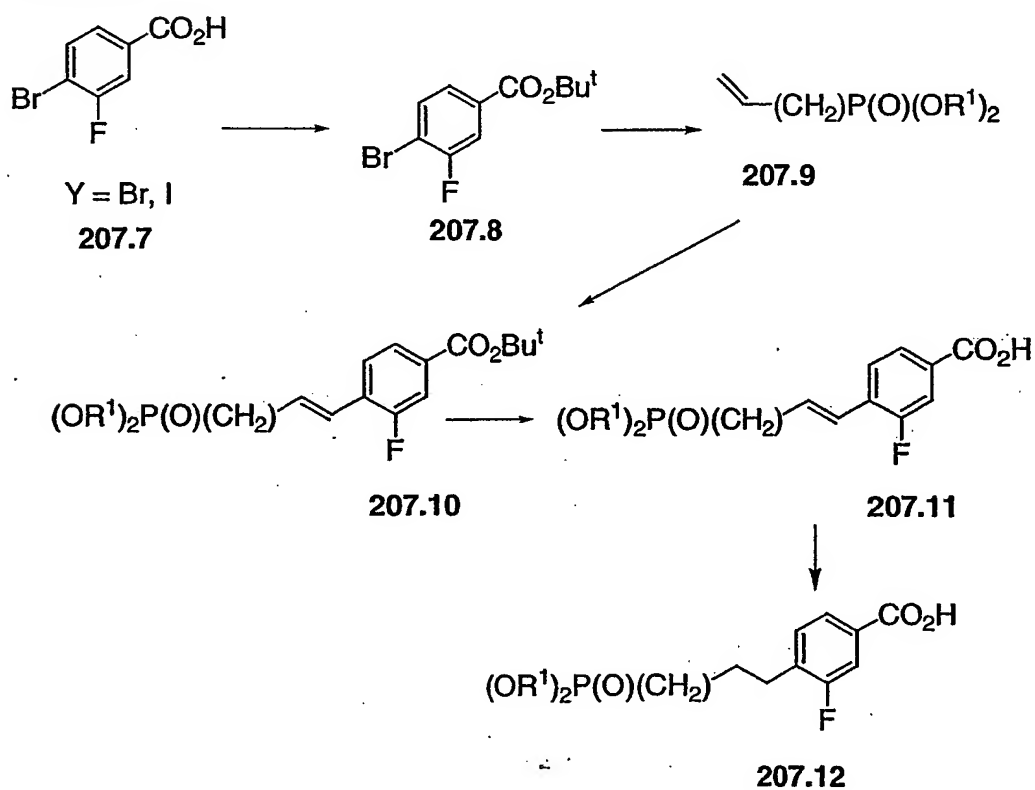
Example



Scheme 207



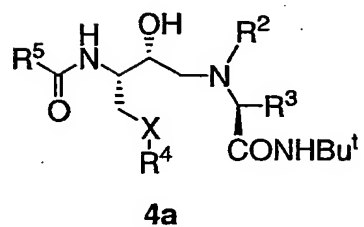
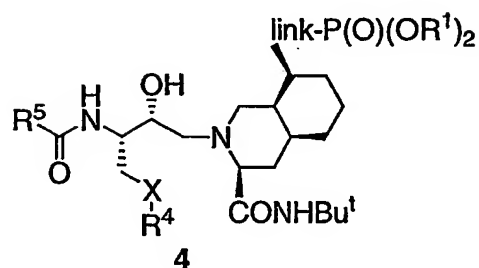
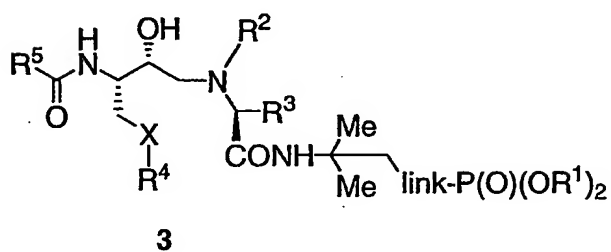
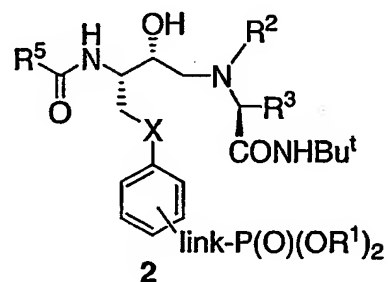
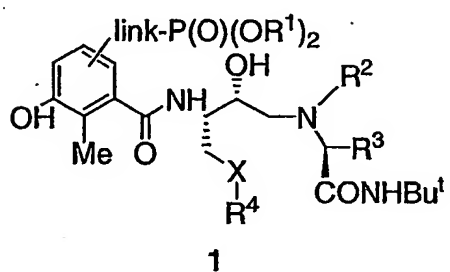
Example



Nelfinavir-like phosphonate protease inhibitors - (NLPPD)

Preparation of the intermediate phosphonate esters.

- 5 The intermediate phosphonate esters **1** to **4a** of this invention are shown in Chart 1. Subsequent chemical modifications, as described herein, permit the synthesis of the final compounds of this invention.
- The structures of the amine components $R^2NHCH(R^3)CONHBu^t$ **6-20e** are shown in Chart 2. Although specific stereoisomers of some of the amines are shown, all stereoisomers of the
- 10 amine components are utilized. Chart 2 also illustrates that, in addition to the tert. butyl amines **5**, the corresponding 2,2,2-trifluoroethyl and 2-methylbenzyl amides are utilized in the synthesis of the phosphonate intermediate compounds of this invention.
- Chart 3 depicts the structures of the R^4 components **21-26**. Charts **4a-4c** illustrate the structures of the carboxylic acid components R^5COOH , **C1-C49**.
- 15 The intermediate compounds **1** to **4a** incorporate a phosphonate moiety connected to the a nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts 5 and 5a illustrate examples of the linking groups **38-59** present in the structures **1-4a**, and in which "etc" refers to the scaffold, e.g., nelfinavir.
- Schemes 1 - 50 illustrate the syntheses of the intermediate phosphonate compounds of this
- 20 invention, **1-4a**, and of the intermediate compounds necessary for their synthesis.

Chart 1. Structures of phosphonate ester intermediate compounds

$R^1 = \text{H, alkyl, alkenyl, aryl, aralkyl}$

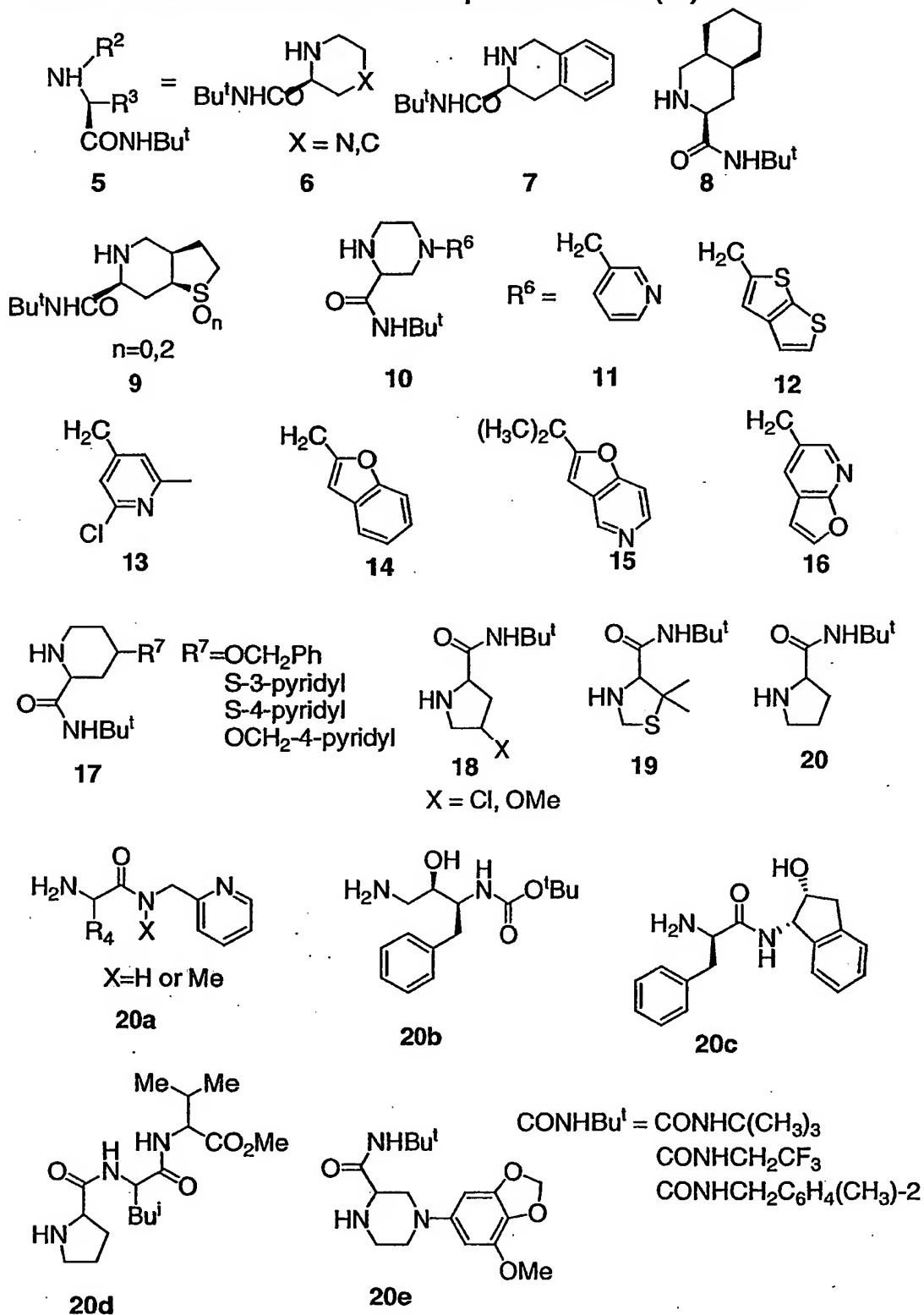
Chart 2. Structures of the amine component $R^2NHCH(R^3)CONHBu^t$ 

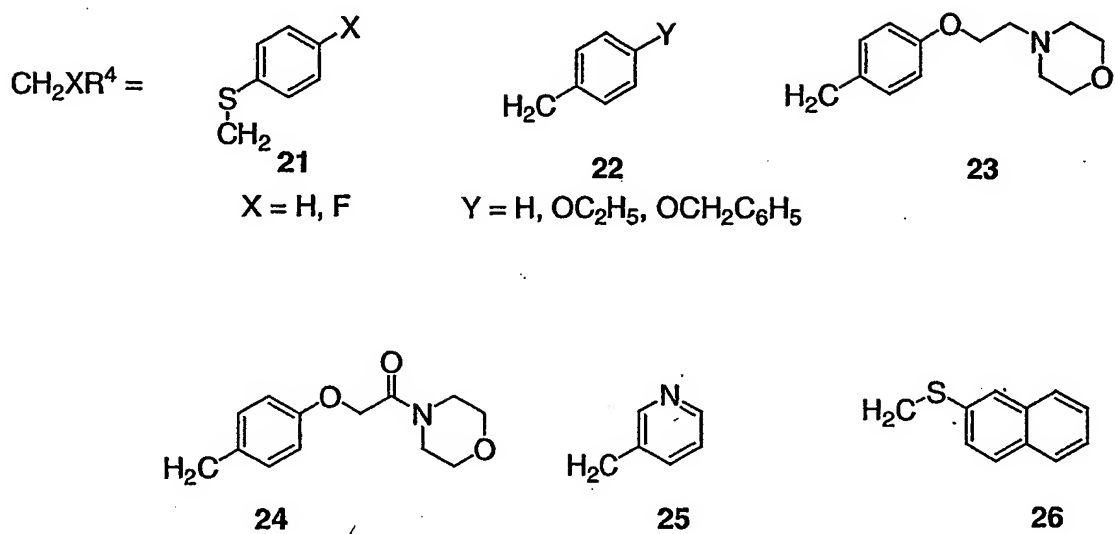
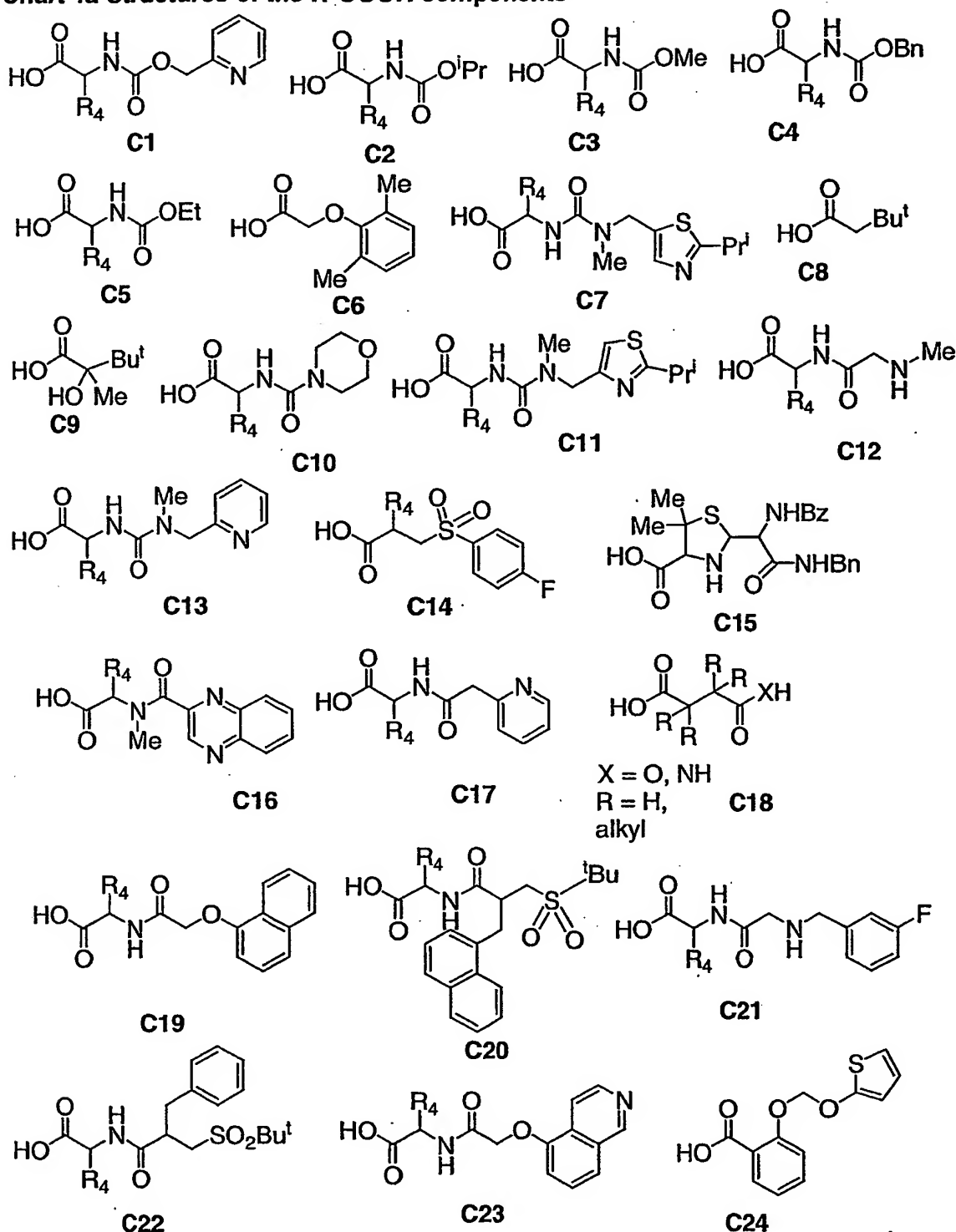
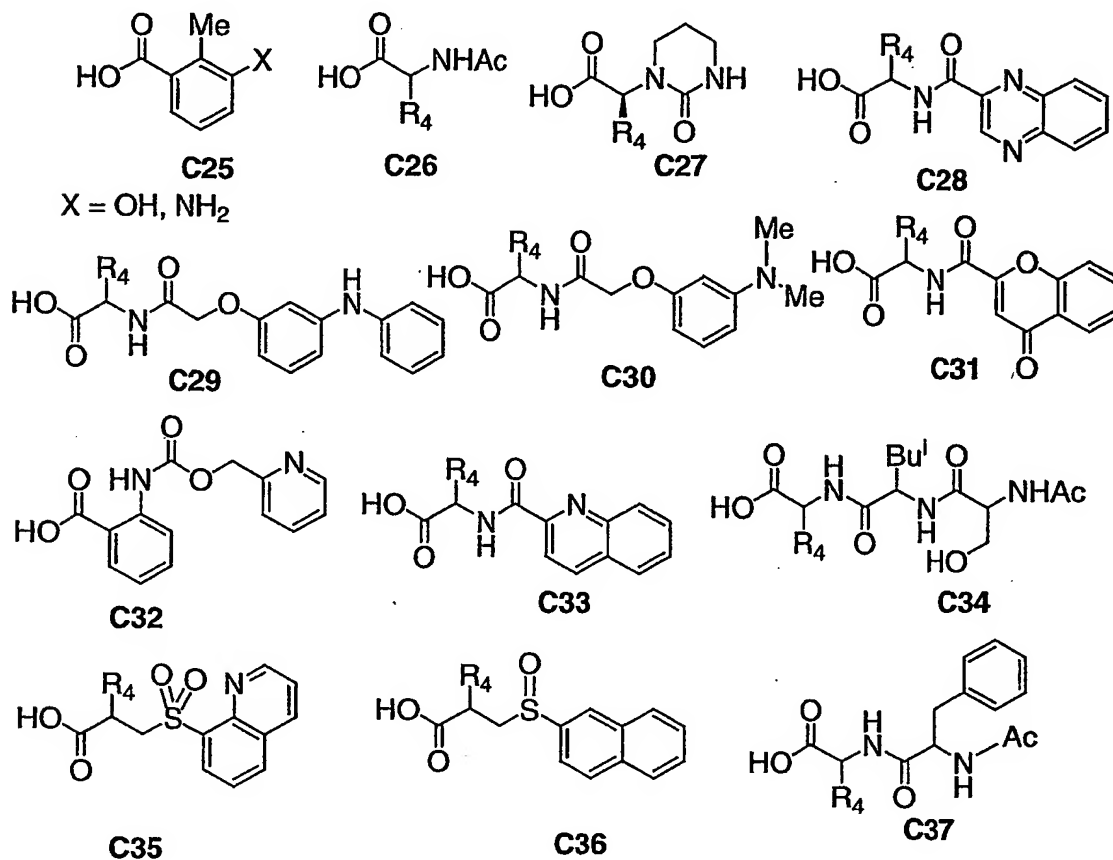
Chart 3. Structures of the R⁴ components

Chart 4a Structures of the R⁵COOH components

R⁴ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

Chart 4b Structures of the R⁵COOH components

R⁴ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

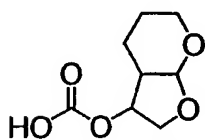
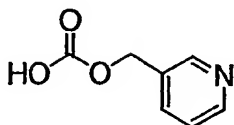
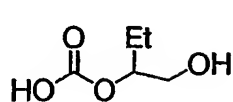
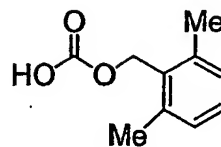
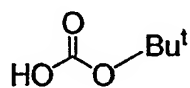
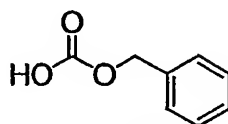
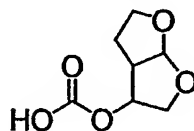
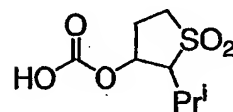
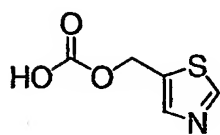
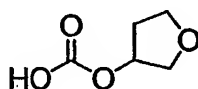
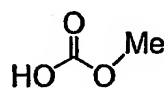
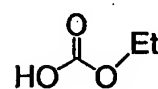
Chart 4c Structures of the R⁵COOH components**C38****C39****C40****C41****C42****C43****C44****C45****C46****C47****C48****C49**

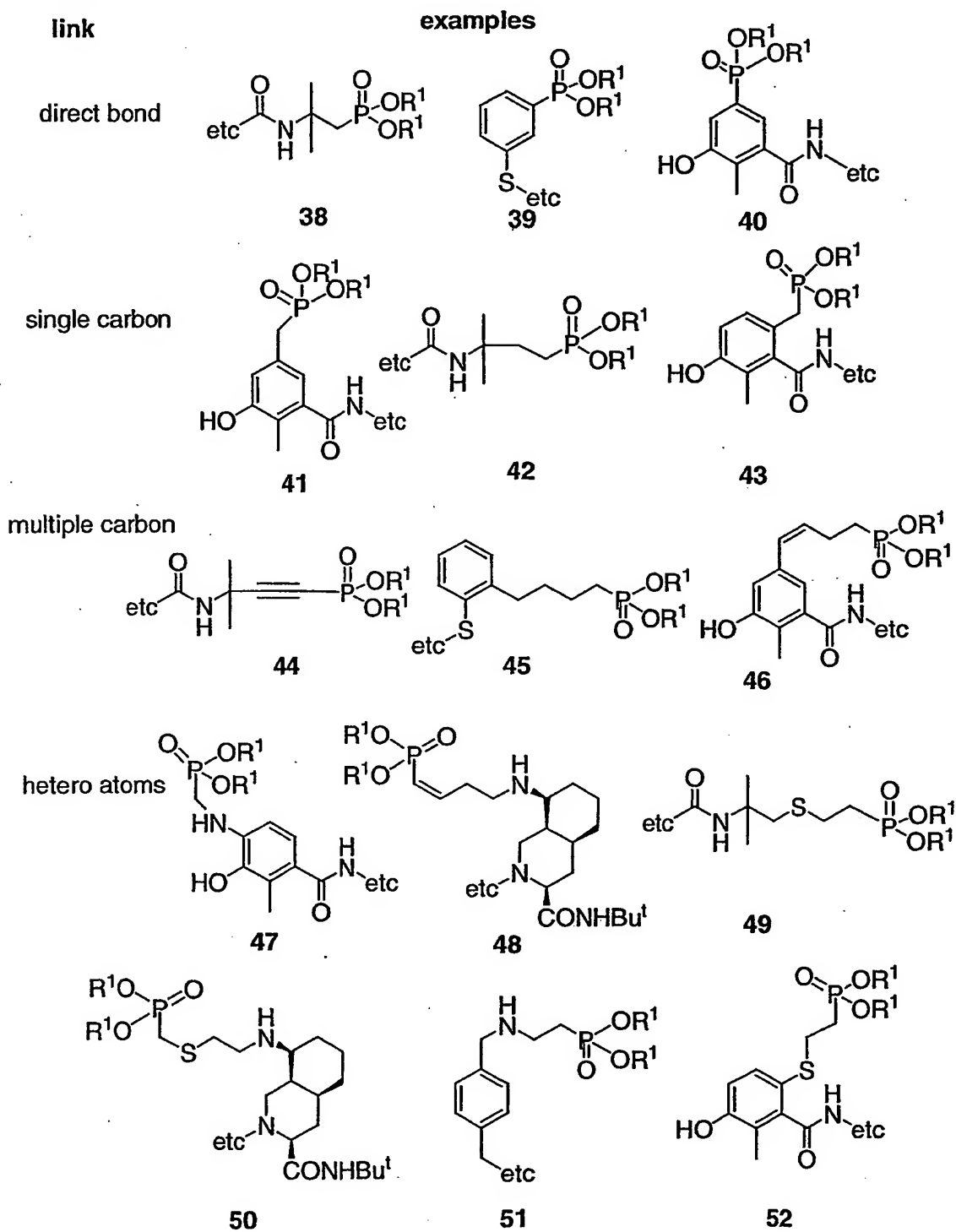
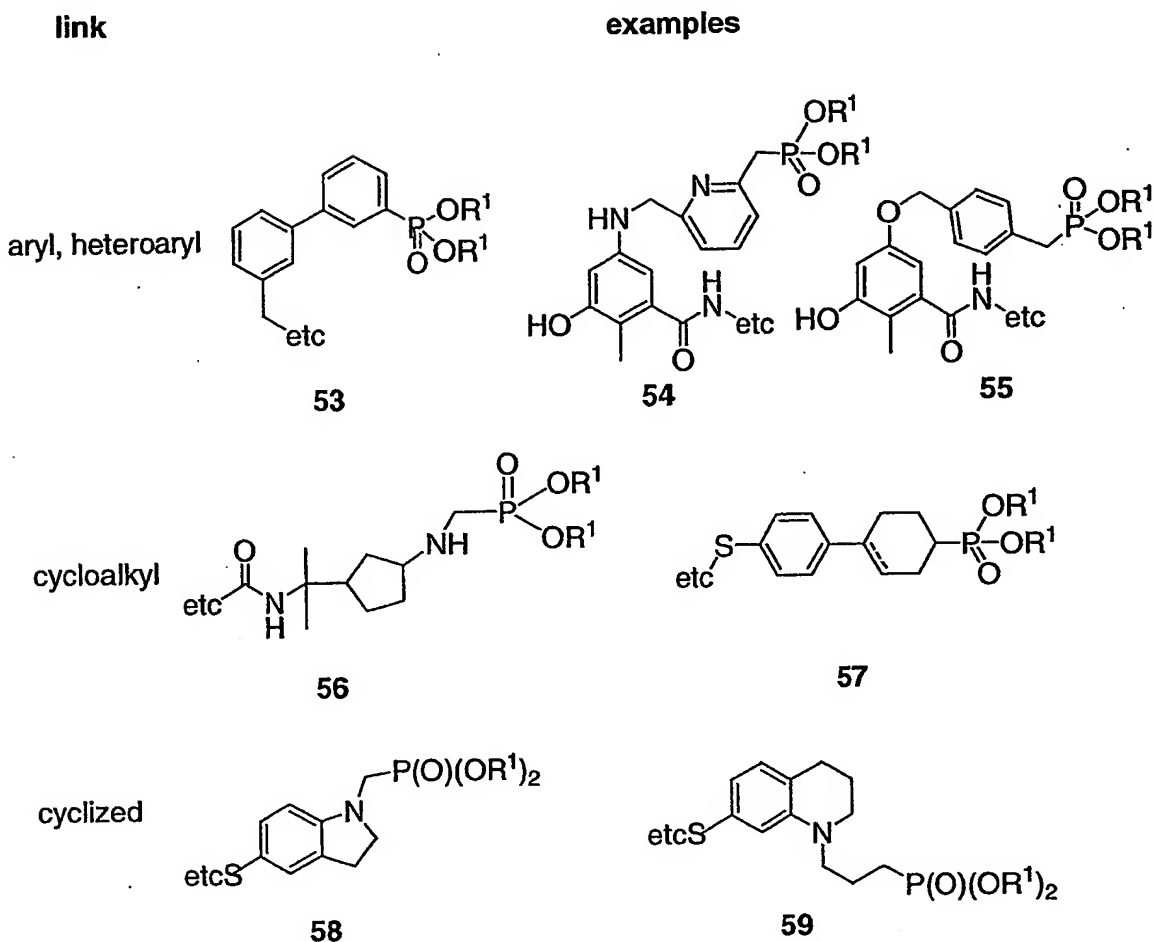
Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.

Chart 5a Examples of the linking group between the scaffold and the phosphonate moiety.**Protection of reactive substituents.**

5

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M Wuts, Second Edition 1990.

10 Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate intermediates 1, in which X=S.

The syntheses of the phosphonates 1 in which X=S, and in which the group link-P(O)(OR¹)₂ is attached to the benzoic acid moiety, are shown in Schemes 1- 3.

5 Scheme 1 illustrates the preparation of the phosphonate intermediate compounds 1, or precursors thereto. 4-Amino-tetrahydro-furan-3-ol 60, the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with the carboxylic acid 61, or an activated derivative thereof, the preparations of which are described below, to form the amide 62.

10 The preparation of amides by reaction of carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p 274. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

15 Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride or anhydride, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

Preferably, the carboxylic acid is first converted into the acid chloride by reaction with, for example, thionyl chloride, oxalyl chloride and the like. The acid chloride 61, in which X is Cl, 20 is then reacted with an equimolar amount of the amine 60, in the presence of a weak inorganic base such as sodium bicarbonate, in an aprotic solvent such as dichloromethane, at ambient temperature, to afford the amide 62.

The hydroxyl group on the tetrahydrofuran moiety so obtained is converted into a leaving group such as p-toluenesulfonyl or the like, by reaction with a sulfonyl chloride in an aprotic 25 solvent such as pyridine or dichloromethane.

Preferably, the hydroxy amide 62 is reacted with an equimolar amount of methanesulfonyl chloride in pyridine, at ambient temperature, to afford the methanesulfonyl ester 63.

The product 63, bearing a suitable sulfonyl ester leaving group, is then subjected to acid-catalyzed rearrangement to afford the isoxazoline 64. The rearrangement reaction is 30 conducted in the presence of an acylating agent such as a carboxylic anhydride, in the presence of a strong acid catalyst.

Preferably, the mesylate **63** is dissolved in an acylating agent such as acetic anhydride at about 0°, in the presence of about 5 mole % of a strong acid such as sulfuric acid, to afford the isoxazoline mesylate **64**.

5 The leaving group, for example a mesylate group, is next subjected to a displacement reaction with an amine.

The compound **64** is reacted with an amine **5**, as defined in Chart 2, in a protic solvent such as an alcohol, in the presence of an organic or inorganic base, to yield the displacement product **65**.

10 Preferably, the mesylate compound **64** is reacted with an equimolar amount of the amine **5**, in the presence of an excess of an inorganic base such as potassium carbonate, at ambient temperature, to afford the product **65**.

The isoxazoline compound **65** is then reacted with a thiol R⁴SH **66**, in which R⁴ is phenyl, 4-fluorophenyl or 2-naphthyl, as shown in Chart 3, to afford the thioether **1**. The reaction is conducted in a polar solvent such as DMF, pyridine or an alcohol, in the presence of a weak
15 organic or inorganic base, to afford the product **1**.

Preferably, the isoxazoline **65** is reacted, in methanol, with an equimolar amount of the thiol R⁴SH **66**, in the presence of an excess of a base such as potassium bicarbonate, at ambient temperature, to afford the thioether **1**.

20 Alternatively, the compounds **1** can be obtained by means of the reactions shown in Scheme 2. In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, **67**, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol R⁴SH **66**, as defined above, to afford the thioether **68**.

The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the
25 like, in the presence of an inorganic or organic base, at from 0° to 80°, for from 1-12 hours, to afford **68**.

Preferably the mesylate **67** is reacted with an equimolar amount of the thiol R⁴SH **66**, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic
30 base such as sodium hydroxide, at about 50°, to give the product **68**.

The 1,3-dioxolane protecting group present in the compound **68** is removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol **69**. Methods

for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M Wuts, Second Edition 1990, p. 191.

For example, the 1,3-dioxolane compound 68 is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture.

- 5 Preferably, the 1,3-dioxolane 68 is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°, to yield the product 69.

The primary hydroxyl group of the diol 69 is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as

- 10 dichloromethane and the like, in the presence of an inorganic or organic base.

Preferably, equimolar amounts of the diol 69 and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the ester 70.

- The hydroxy ester 70 is next reacted with a sulfonyl chloride such as methanesulfonyl chloride, 15 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the corresponding sulfonyl ester 71.

Preferably, equimolar amounts of the carbinol 70 and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the mesylate 71.

- The compound 71 is then subjected to a hydrolysis-cyclization reaction to afford the oxirane 20 72.

The mesylate or analogous leaving group present in 71 is displaced by hydroxide ion, and the carbinol thus produced, without isolation, spontaneously transforms into the oxirane 72 with elimination of 4-nitrobenzoate. To effect this transformation, the sulfonyl ester 71 is reacted with an alkali metal hydroxide or tetraalkylammonium hydroxide in an aqueous organic

- 25 solvent.

Preferably, the mesylate 71 is reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour, to afford the oxirane 72.

The oxirane compound 72 is then subjected to regiospecific ring-opening reaction by treatment with an amine 5, to give the aminoalcohol 73.

- 30 The amine and the oxirane are reacted in a protic organic solvent, optionally in the additional presence of water, at 0° to 100°, and in the presence of an inorganic base, for 1 to 12 hours, to give the product 73.

Preferably, equimolar amounts of the reactants **5** and **72** are reacted in aqueous methanol at about 60° in the presence of potassium carbonate, for about 6 hours, to afford **73**.

The carbobenzyloxy (cbz) protecting group in the product **73** is removed to afford the free amine **74**. Methods for removal of cbz groups are described, for example, in Protective

5 Groups in Organic Synthesis, by T.W. Greene and P.G. M. Wuts, Second Edition, p. 335.

The methods include catalytic hydrogenation and acidic or basic hydrolysis.

For example, the cbz-protected amine **73** is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or alcoholic solvent, to yield the free amine **74**.

Preferably, the cbz group is removed by the reaction of **73** with potassium hydroxide in an

10 alcohol such as isopropanol at ca. 60° to afford the amine **74**.

The amine **74** so obtained is next acylated with a carboxylic acid or activated derivative **61**, using the conditions described above for the conversion of **60** to **62**, to yield the final amide product **75**.

The reactions shown in the above-described Schemes 1 and 2 depict the preparation of

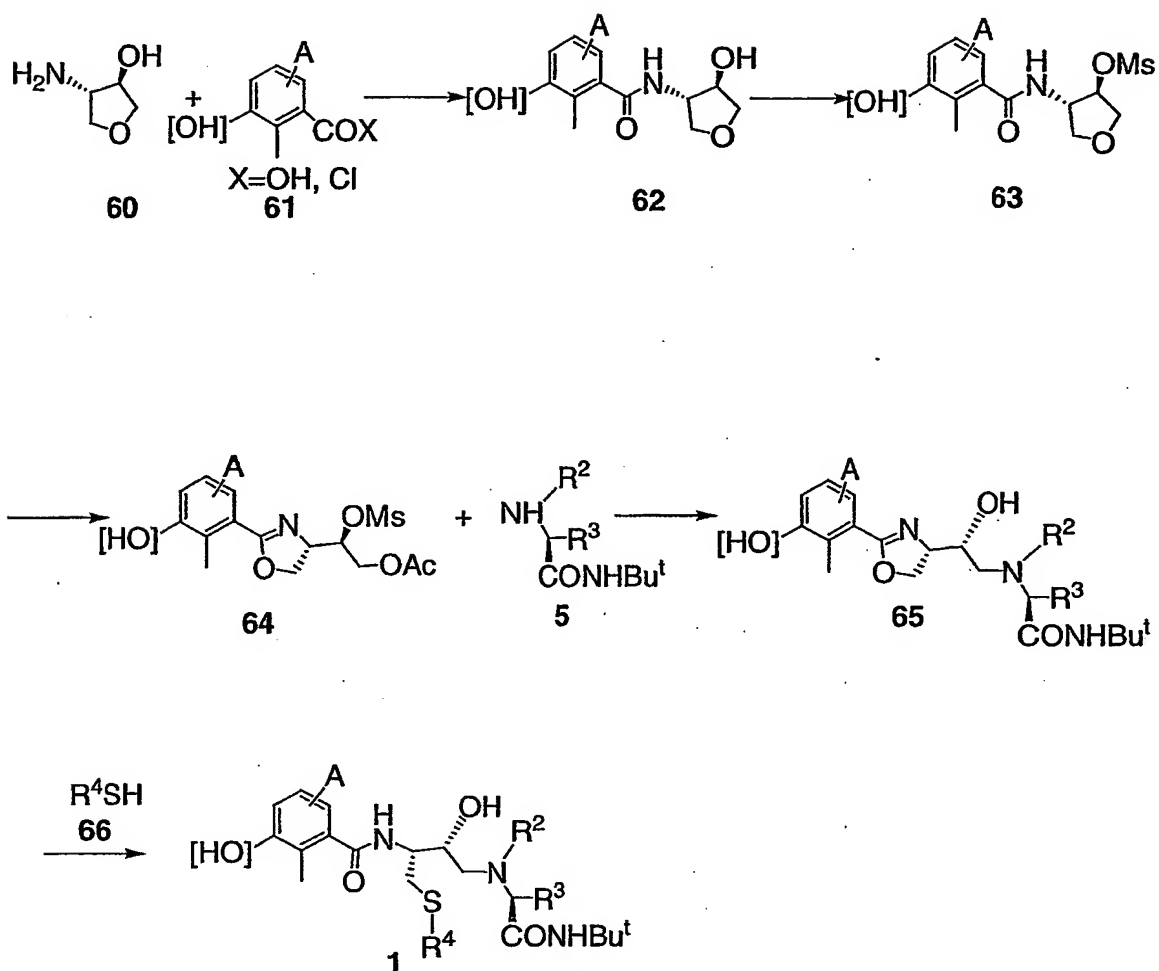
15 intermediates **1** in which A is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme 3 shows the conversion of the compounds **75** in which A is OH, SH, NH, to the compounds **1** in which A is link-P(O)(OR¹)₂.

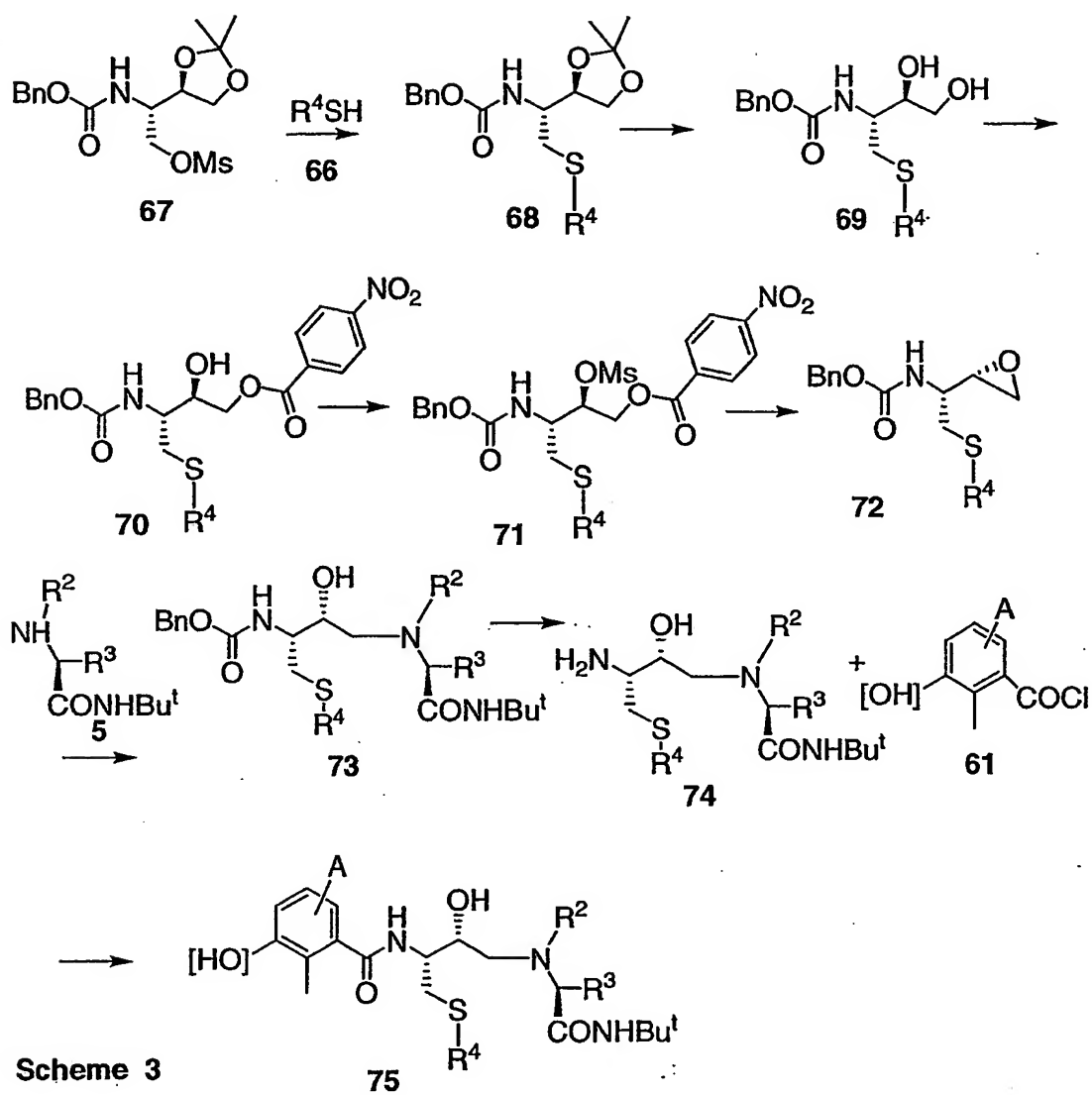
Methods for these transformations are described below, Schemes 20-48, in the descriptions of

20 the preparations of the phosphonate-containing reactants.

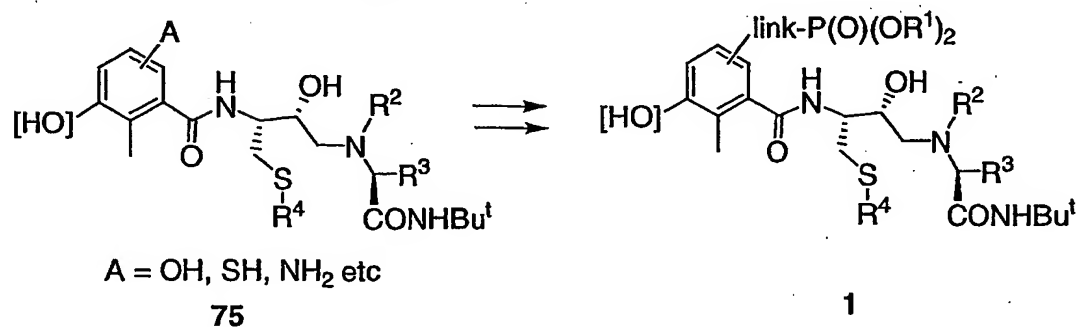
Scheme 1


$$A = \text{link-(P)(OR}^1)_2 \text{ or } A = \text{OH, SH, NH, etc}$$

Scheme 2



Scheme 3



Preparation of the phosphonate intermediates 2, in which X = S.

The synthesis of the phosphonate compounds 2 in which the link-P(O)(OR¹)₂ group is attached to the phenylthio moiety, is shown in Scheme 4.

In this sequence, 4-amino-tetrahydro-furan-3-ol, 60, the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with a carboxylic acid or activated derivative thereof,

- 5 R⁵COX, 76, using the conditions described above for the preparation of the amide 62, Scheme 1, to afford the amide 77. The compounds 77, and analogous acylation products described below, in which the carboxylic acid R⁵COOH is one of the carbonic acid derivatives C36-C49, as defined in Chart 4c, are carbamates. Methods for the preparation of carbamates are described below, (Scheme 50).

- 10 The amide product 77 is then transformed, using the sequence of reactions shown in Scheme 4, into the isoxazoline compound 80. The conditions for this sequence of transformations are the same as those described for the preparation of the isoxazoline 65 in Scheme 1.

- The isoxazoline compound 80 is then reacted with a thiol compound 66, in which the
15 substituent A is either the group link-P(O)(OR¹)₂, or a precursor thereto, such as OH, SH, NH, as described herein, to afford the thioether 81.

The conditions for this reaction are the same as those described above for the preparation of the thioether 1, (Scheme 1).

- Alternatively, the thioether 81 can be prepared by the sequence of reactions shown in Scheme
20 5. In this sequence, the previously described 1,3-dioxolane mesylate compound 67 is reacted with a thiol compound 66 in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor thereto, such as OH, SH, NH, as described herein, to afford the thioether 82. The conditions for this reaction are the same as those described above for the preparation of the thioether 68, (Scheme 2).

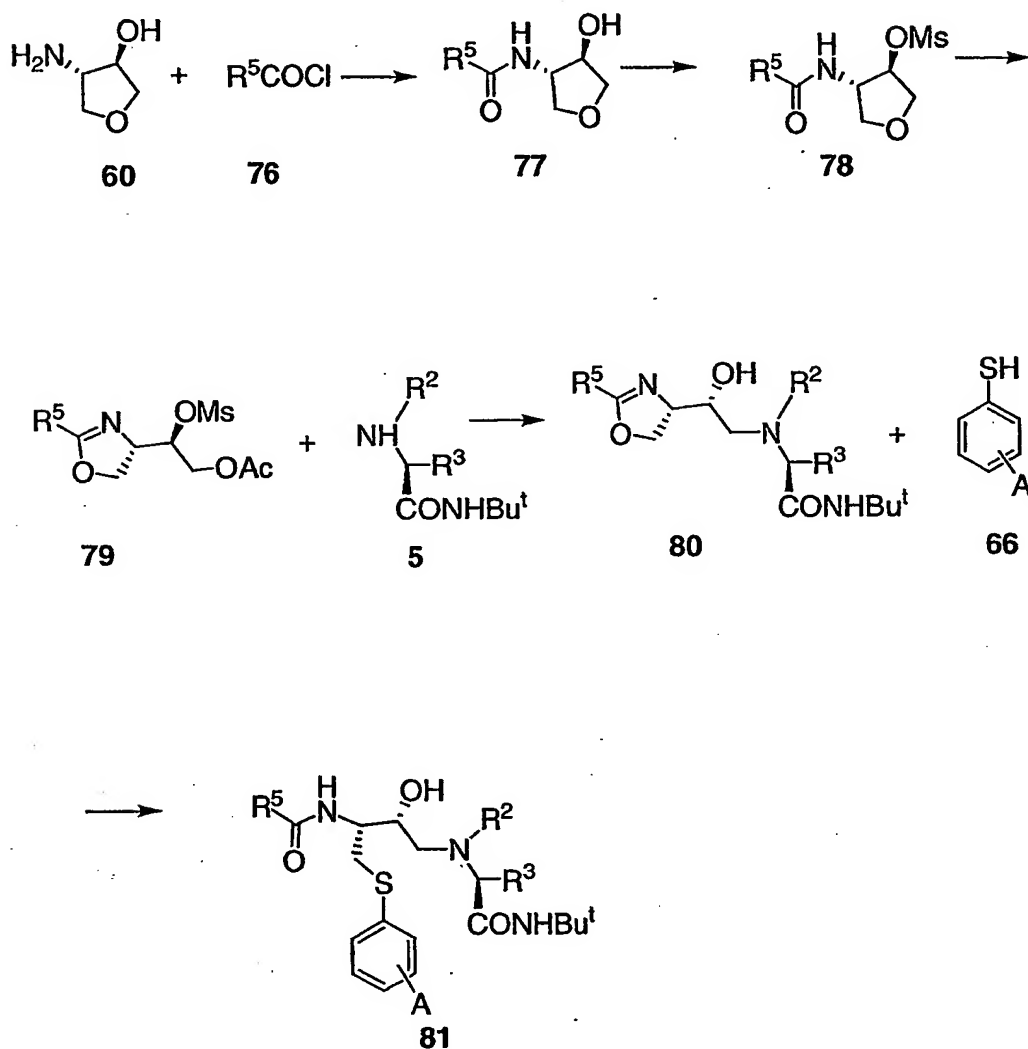
- 25 The thus-obtained thioether 82 is then transformed, using the sequence of reactions shown in Scheme 2 into the compound 81.

The reactions shown in the above-described Schemes 4 and 5 depict the preparation of intermediates 81 in which A is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

- 30 Scheme 6 shows the conversion of the compounds 81 in which A is OH, SH, NH, into the compounds 2 in which A is link-P(O)(OR¹)₂.

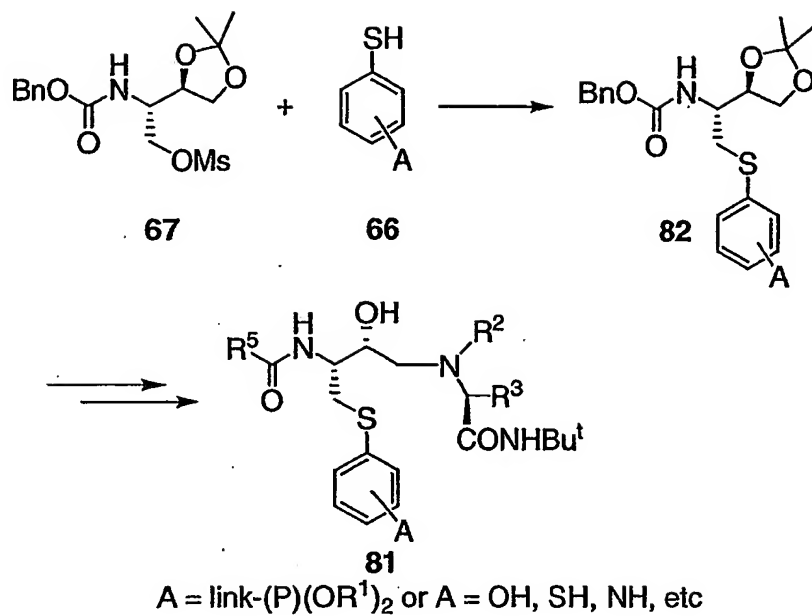
Methods for these transformations are shown in Schemes 20-48 and are discussed in the descriptions of the preparations of the phosphonate-containing reactants.

Scheme 4

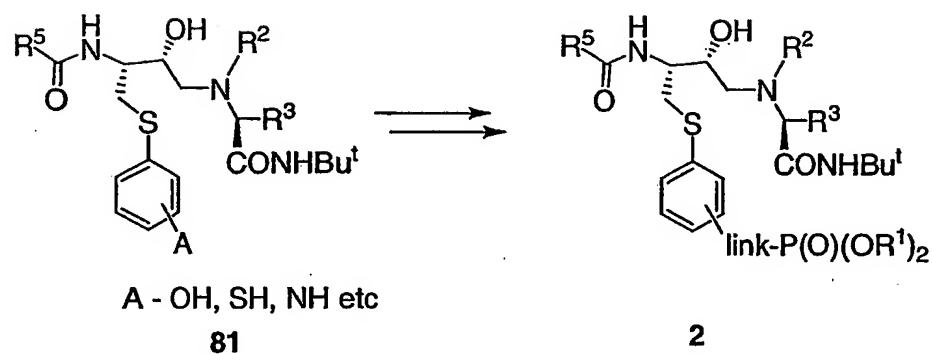


A = link-(P)(OR¹)₂ or A = OH, SH, NH, etc.

Scheme 5



Scheme 6



Preparation of the phosphonate intermediates 3, in which X = S.

The phosphonate intermediates 3 in which X = S, and in which the link-P(O)(OR¹)₂ group is attached to the tert. butyl moiety, are prepared as shown in Schemes 7 and 8.

As shown in Scheme 7, the isoxazolines **79**, the preparation of which are described above, are reacted with the amines **83**, using the conditions described above for the conversion of **64** to **65**, (Scheme 1) to afford the product **84**.

This compound is then converted, using the methods described above, (Scheme 1) into the compound **85**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Alternatively, the compounds **85** can be prepared by the reactions shown in Scheme 8.

In this method, the oxirane **72**, the preparation of which is described above, (Scheme 2) is reacted with the amine **83**, using the reaction conditions described above for the conversion of **72** to **73** (Scheme 2), to afford the hydroxyamine **86**. This compound is then converted, using the procedures described above, into the compound **85**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

The reactions shown in the above-described Schemes 7 and 8 depict the preparation of intermediates **85** in which A is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme 9 shows the conversion of the compounds **85** in which A is OH, SH, NH, into the compounds **3** in which A is link-P(O)(OR¹)₂.

Methods for these transformations are described below in Schemes 20 to 48 in which the preparations of the phosphonate-containing reactants are depicted.

Preparation of the phosphonate intermediates **4** in which X = S.

The preparations of the phosphonate intermediates **4**, in which the link-P(O)(OR¹)₂ group is attached to the decahydroisoquinoline moiety, are shown in Schemes 10 to 12.

As shown in Scheme 10, the isoxazoline mesylate **79**, the preparation of which is described above, (Scheme 4) is reacted with the amine **88**, the preparation of which is described below. The reaction is preformed using the procedures described above for the preparation of **65** (Scheme 1).

The reaction product **89** is then transformed, using the procedures described above, (Scheme 1) into the compound **90**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Alternatively, the compound **90** can be prepared by the reactions shown in Scheme 11.

In this reaction scheme, the oxirane 72, the preparation of which is described above, (Scheme 2) is reacted with the amine 88, using the conditions described above for the preparation of 73 (Scheme 2) to afford the hydroxyamine 91. This compound is then converted, using the reaction schemes and conditions described above for the preparation of 1, (Scheme 2) into the compound 90, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

The reactions shown in the above-described Schemes 10 and 11 depict the preparation of intermediates 90 in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme 12 shows the conversion of the compounds 90 in which B is OH, SH, NH, to the compounds 4 in which A is link-P(O)(OR¹)₂.

Methods for these transformations are described below in Schemes 20-48 in which the preparations of the phosphonate-containing reactants are depicted.

Preparation of the phosphonate intermediates 1, in which X is a direct bond

As shown in Scheme 13, the oxirane 92, in which X is H, the preparation of which is described in J. Med. Chem., 1997, 40, 1995, and in Bioorg. Med. Chem. Lett., 5, 2885, 1995, is reacted with the amine 5. The compounds are reacted together using the conditions described above for the preparation of 73, (Scheme 2) to afford the hydroxyamine 93. This compound is then transformed, using the procedures described above for the preparation of 1, (Scheme 2) into the compound 94, in which A is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme 14 shows the conversion of the compounds 94 in which A is OH, SH, NH, to the compounds 1 in which A is link-P(O)(OR¹)₂.

Methods for these transformations are described below in Schemes 20-43 in which the preparations of the phosphonate-containing reactants are depicted.

Preparation of the phosphonate intermediates 2, in which X is a direct bond.

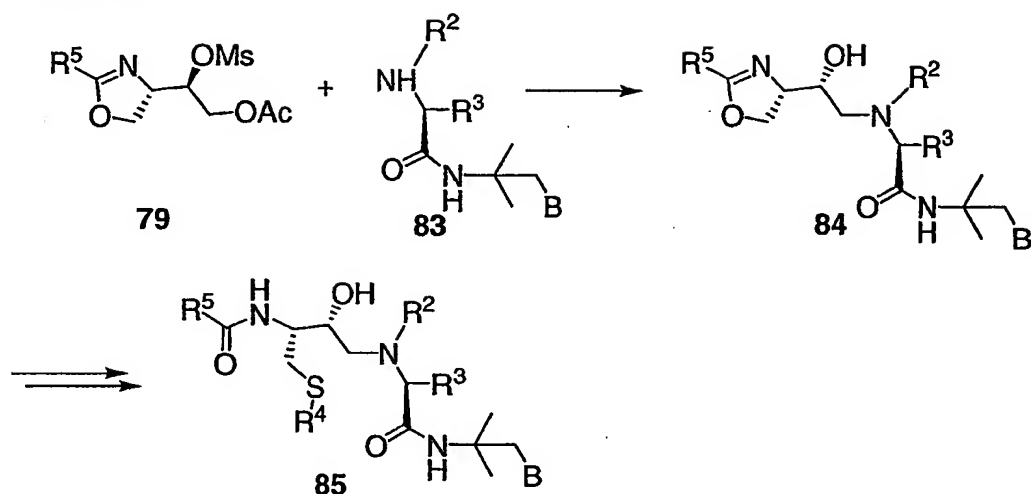
The preparation of the compounds 2, in which X is a direct bond, and the group link-P(O)(OR¹)₂ is attached to the phenyl ring, is illustrated in Schemes 14a and 14b.

In the procedure shown in Scheme 14a, the epoxide 14a-1, prepared as described below (Scheme 45) is reacted with an amine 5, using the conditions described above for the preparation of the hydroxyamine 73 (Scheme 2), to afford the hydroxyamine 14a-2.

The latter compound, after removal of the BOC protecting group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M. Wuts, Third Edition 1999, p. 520-522, is then converted, by reaction with the carboxylic acid R^5COOH , or an activated derivative thereof, into the amide 14a-3. The conditions for this reaction are the same as those described above for the preparation of the amide 62, (Scheme 1).

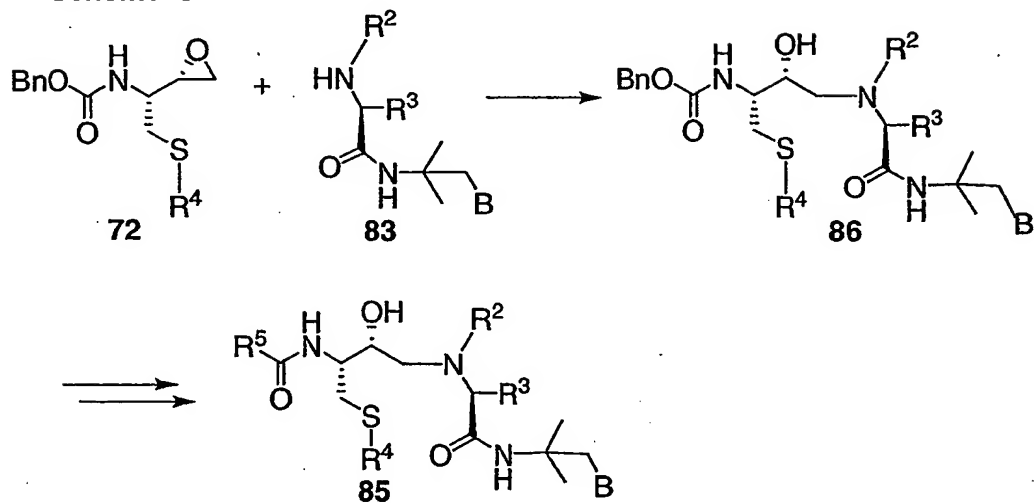
The reactions shown in Scheme 14a illustrate the preparation of the compounds 14a-3 in which A is either the group link-P(O)(OR¹)₂ or a precursor thereto such as OH, SH, NH₂. Scheme 14b illustrates the conversion of the compounds 14a-3, in which A is OH, SH, NH₂, into the compounds 2 in which A is the group link-P(O)(OR¹)₂. The methods for this transformation are described below in Schemes 20-48, in which the preparation of the phosphonate-containing reactants are described.

Scheme 7



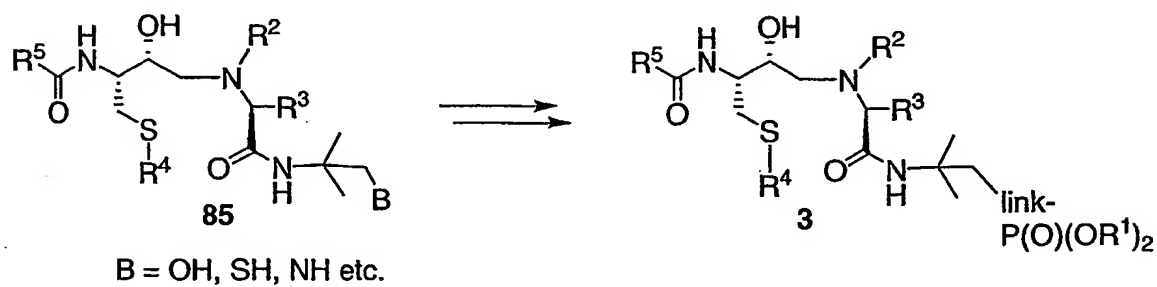
$B = \text{link}-(P)(OR^1)_2$ or $B = OH, SH, NH$ etc.

Scheme 8



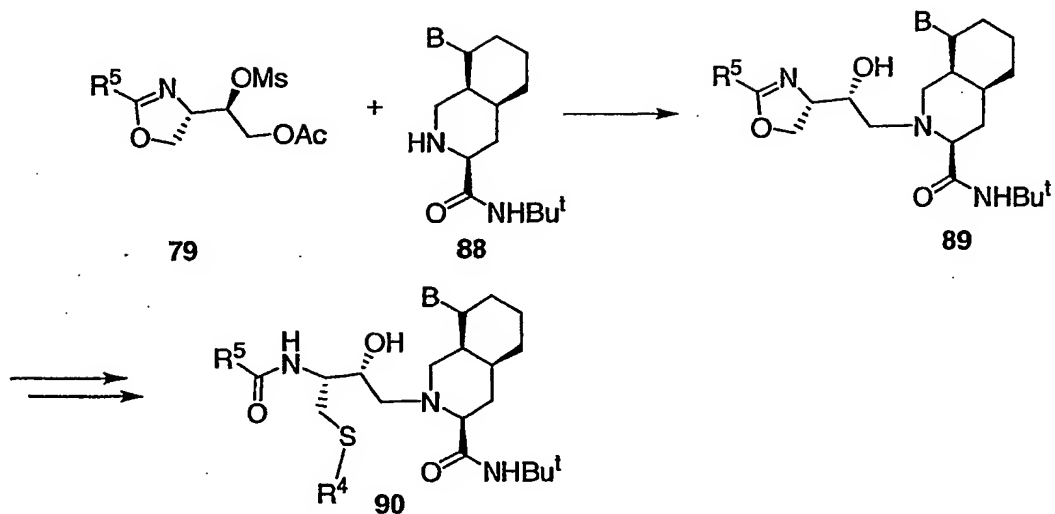
$B = \text{link}-(P)(OR^1)_2$ or $B = OH, SH, NH$ etc.

Scheme 9



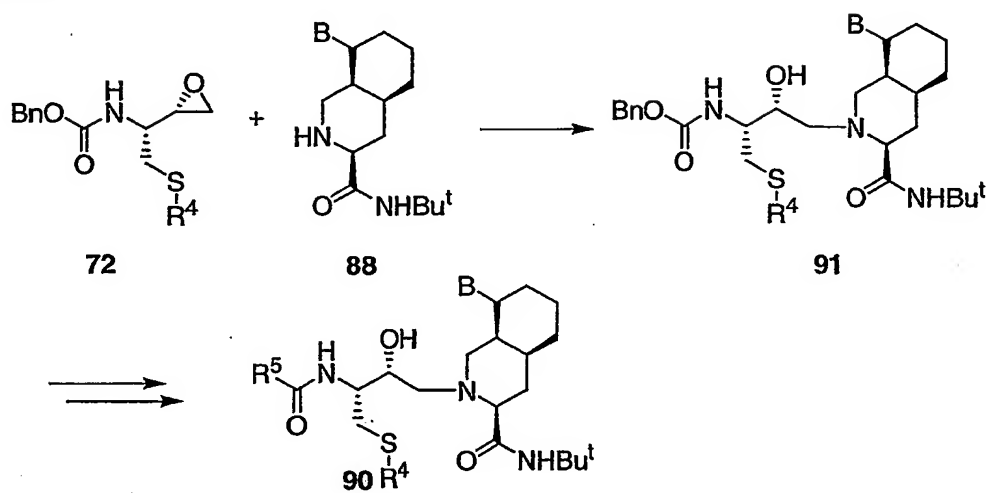
$B = OH, SH, NH$ etc.

Scheme 10



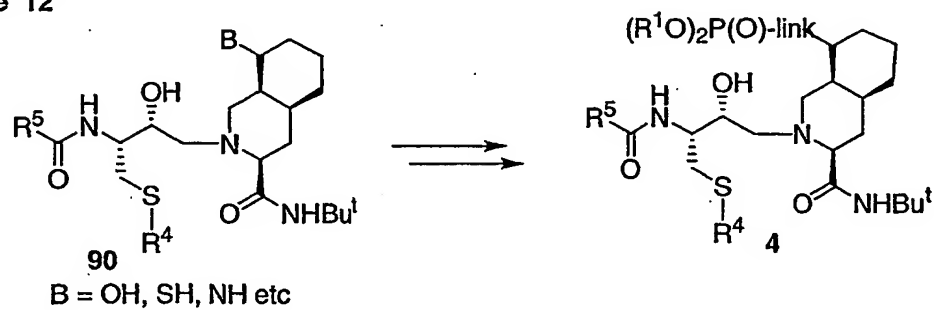
B = link-(P)(OR¹)₂ or B = OH, SH, NH etc

Scheme 11

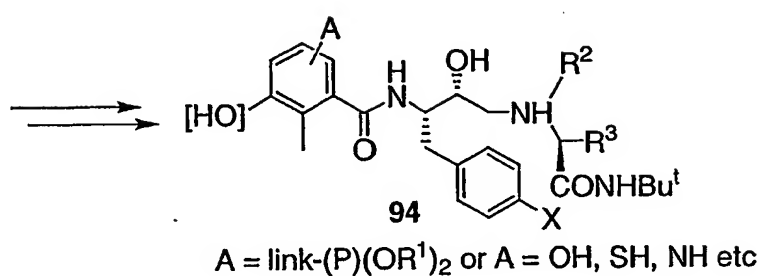
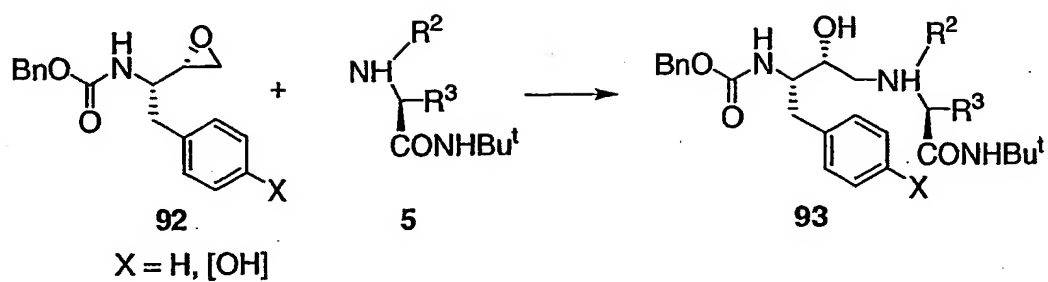


B = link-(P)(OR¹)₂ or B = OH, SH, NH etc

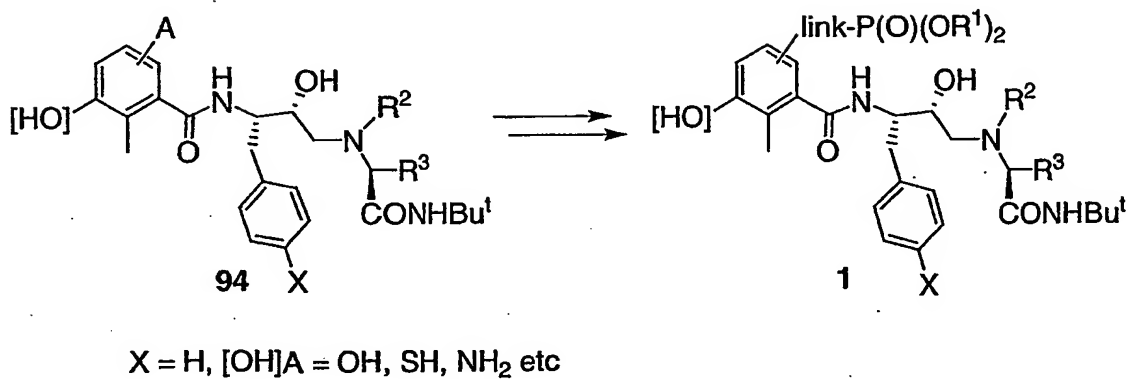
Scheme 12



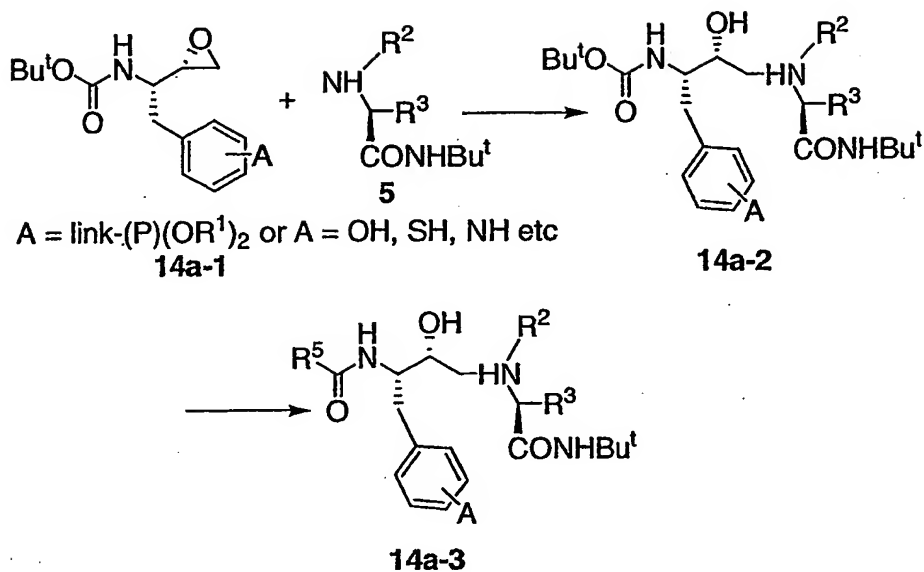
Scheme 13



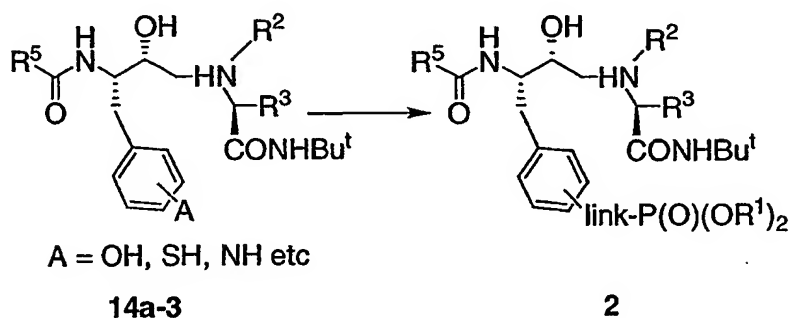
Scheme 14



Scheme 14a



Scheme 14b

**Preparation of the phosphonate intermediates 3, in which X is a direct bond.**

As shown in Scheme 15, the oxirane **92**, in which X is H, is reacted with the amine **83**, in which the phosphonate or precursor group is attached to the tert. butyl group, to afford the product **95**. The conditions for this reaction are the same as described above for the preparation of **73** (Scheme 2). This compound is then transformed, using the procedures described above for the preparation of **1**, (Scheme 2) into the compound **96**, in which B is either $\text{link}-\text{P}(\text{O})(\text{OR}^1)_2$ or precursor groups to $\text{link}-\text{P}(\text{O})(\text{OR}^1)_2$ such as OH, SH, NH, as described herein.

Scheme 16 shows the conversion of the compounds 96 in which B is OH, SH, NH, to the compounds 3 in which B is link-P(O)(OR¹)₂.

Methods for these transformations are described below in Schemes 20-48 in which the preparations of the phosphonate-containing reactants are depicted.

5

Preparation of the phosphonate intermediates 4, in which X is a direct bond.

As shown in Scheme 17, the oxirane 92 is reacted with the amine 88, in which the phosphonate or precursor group is attached to the decahydroisoquinoline moiety, to afford the product 97. The conditions for this reaction are the same as described above for the preparation of 73 (Scheme 2). This compound is then transformed, using the procedures described above for the preparation of 1, (Scheme 2) into the compound 98, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

10

Scheme 18 shows the conversion of the compounds 98 in which B is OH, SH, NH, into the compounds 4 in which B is link-P(O)(OR¹)₂.

15

Methods for these transformations are described below in Schemes 20-48 in which the preparations of the phosphonate-containing reactants are depicted.

Schemes 13-18 illustrate the preparations of the compounds 1, 3 and 4, in which X is a direct bond, and in which the phenyl ring is either unsubstituted or incorporates a protected hydroxyl group at the 4-position.

20

Scheme 19 depicts the synthesis of compounds 1, 3 and 4, in which X is a direct bond, and in which the phenyl ring incorporates different substituents, as described above (Chart 3) in the 4-position.

In this procedure, [2-(4-hydroxy-phenyl)-1-oxiranyl-ethyl]-carbamic acid tert-butyl ester 99, the preparation of which is described in U.S. Patent 5,492,910, is reacted with an appropriate alkylating agent, such as, for example, ethyl iodide, benzyl chloride, bromoethyl morpholine or bromoacetyl morpholine. The reaction is conducted in an aprotic solvent, such as, for example, dichloromethane or dimethylformamide, in the presence of an organic or inorganic base.

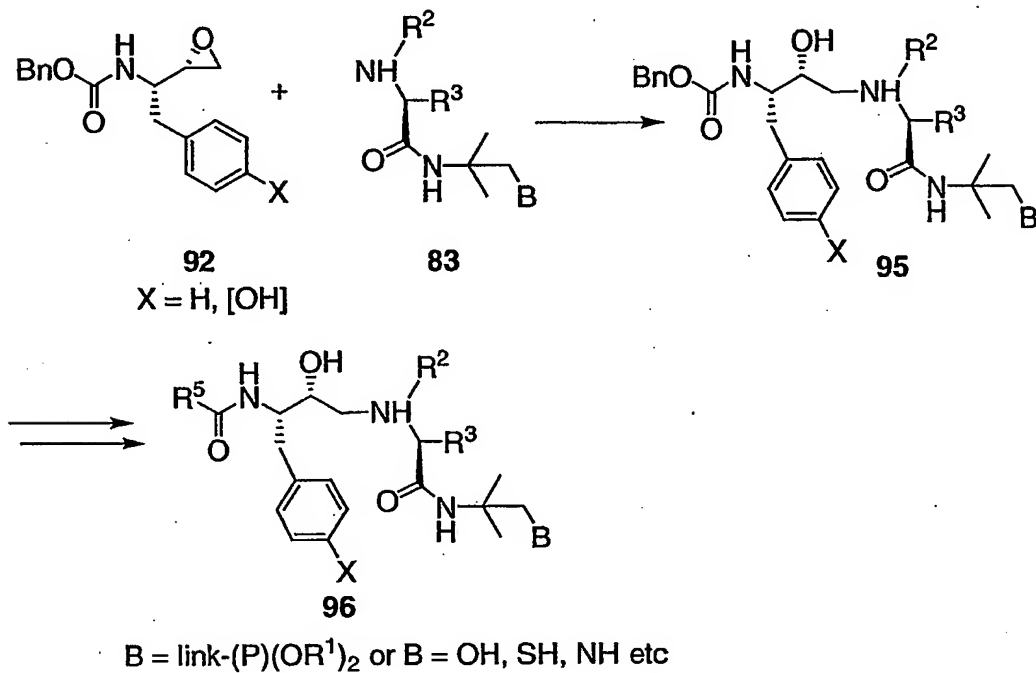
25

Preferably the hydroxy compound 99 is reacted with an equimolar amount of the alkylating agent in dichloromethane, in the presence of diisopropylethylamine, at ambient temperature, so as to afford the ether products 100. The compounds 100 are then transformed, using the

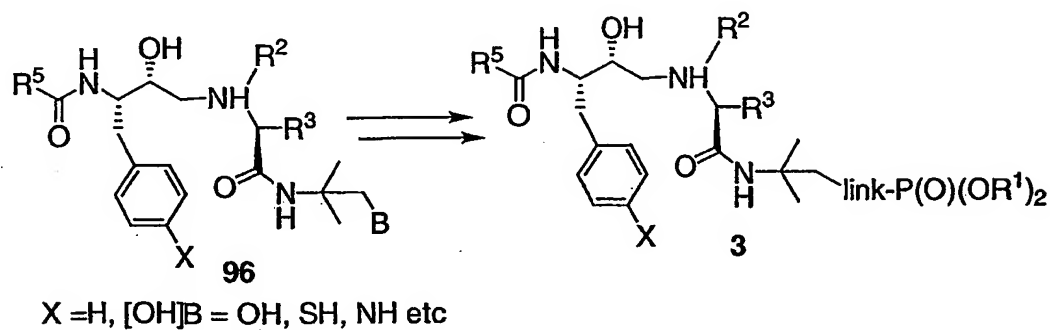
30

conditions described above for the reactions depicted in Schemes 13-18, into the products 1, 3 and 4, in which X is a direct bond, and in which R is as defined in Scheme 19.

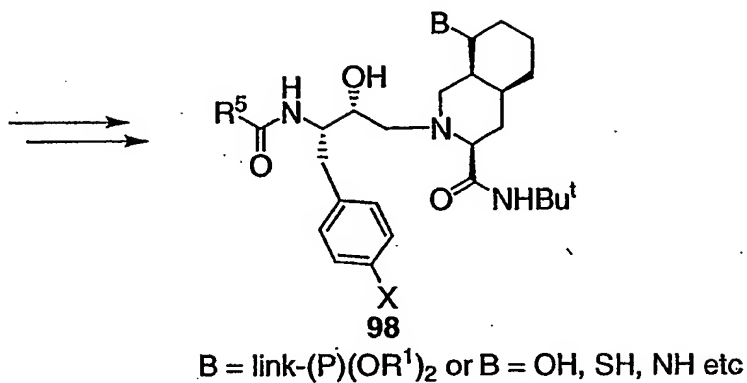
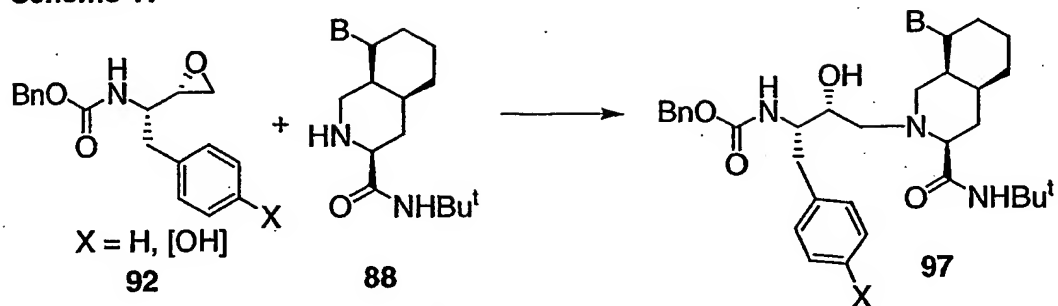
Scheme 15



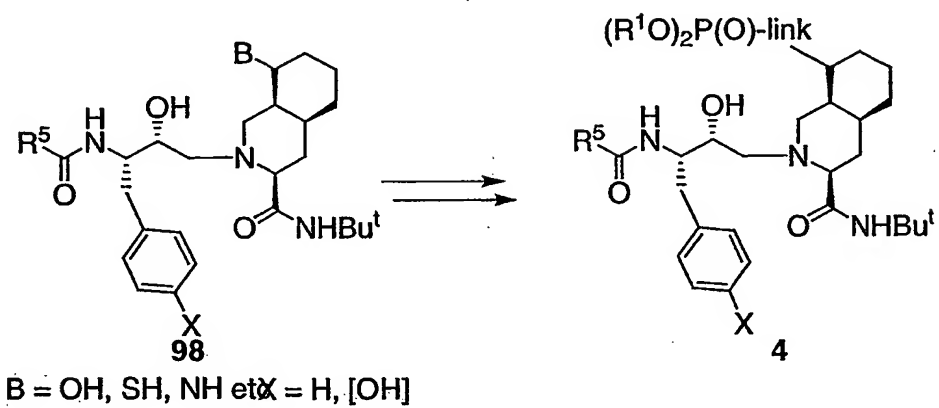
Scheme 16



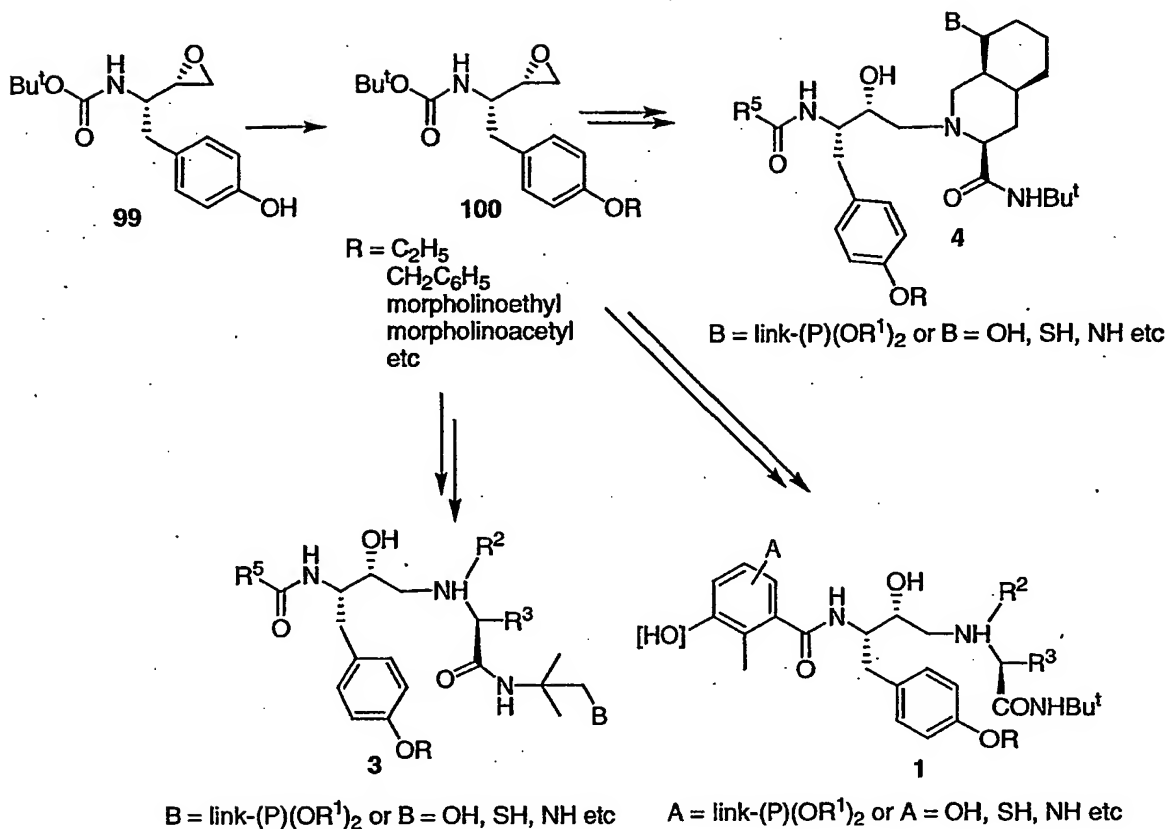
Scheme 17



Scheme 18



Scheme 19



Nel10b.cdx Schemes 19a, 19b

5 Preparation of thiophenol derivatives R^4SH incorporating phosphonate substituents

Various methods for the preparation of thiols are described in *The Chemistry of the Thiol Group*, S. Patai, Ed., Wiley, 1974, Vol. 14, Part 3, p 42.

10 Protection/deprotection of SH groups.

The preparations of thiophenols incorporating phosphonate moieties are shown in Schemes 20-30. In order to avoid unwanted reactions, it may be necessary to protect the SH group, and to deprotect it after the transformations shown. Protected SH groups are shown in the Schemes as [SH]. The protection and deprotection of SH groups is described in a number of publications. For example, in *Protective Groups in Organic Synthesis*, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 277-308, are described the introduction and removal of a

number of SH protecting groups. The selection of a SH protecting group for a given series of reactions requires that it be stable to the reaction conditions employed, and that the protecting group can be removed at the end of the reaction sequence without the occurrence of undesired reactions. In the following descriptions, appropriate protection and deprotection methods are indicated.

Scheme 20 illustrates the preparation of thiophenols in which a phosphonate moiety is attached directly to the aromatic ring.

In this procedure, a halo-substituted thiophenol is subjected to a suitable protection procedure.

10 The protected compound **101** is then coupled, under the influence of a transition metal catalyst, with a dialkyl phosphite **102**, to afford the product **103**. The product is then deprotected to afford the free thiophenol **104**.

Suitable protecting groups for this procedure include alkyl groups such as triphenylmethyl and the like. Palladium (0) catalysts are employed, and the reaction is conducted in an inert

15 solvent such as benzene, toluene and the like, as described in J. Med. Chem., 35, 1371, 1992.

Preferably, the 3-bromothiophenol **105** is protected by conversion to the 9-fluorenylmethyl derivative, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

P.G.M. Wuts, Wiley, 1991, p. 284, and the product **106** is reacted in toluene with a dialkyl phosphite in the presence of tetrakis(triphenylphosphine)palladium (0) and triethylamine, to
20 yield the product **108**. Deprotection, for example by treatment with aqueous ammonia in the presence of an organic co-solvent, as described in J. Chem. Soc. Chem. Comm. 1501, 1986, then gives the thiol **109**.

Using the above procedures, but employing, in place of the bromo compound **105**, different bromo compounds **101**, there are obtained the corresponding thiols **104**.

25

Scheme 21 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **101** is metallated, for example by reaction with magnesium or by transmetallation with an

alkyllithium reagent, to afford the metallated derivative **110**. The latter compound is reacted
30 with a halodialkyl phosphate **111** to afford the product **103**.

Preferably, the 4-bromothiophenol **112** is converted into the S-triphenylmethyl (trityl) derivative **113**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **114** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorodiethyl phosphite **115** to afford the phosphonate **116**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **117**.
5 Using the above procedures, but employing, in place of the halo compound **112**, different halo compounds **101**, there are obtained the corresponding thiols **104**.

Scheme 22 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link.
10 In this procedure, a suitably protected methyl-substituted thiophenol is subjected to free-radical bromination to afford a bromomethyl product **118**. This compound is reacted with a sodium dialkyl phosphite **119** or a trialkyl phosphite, to give the displacement or rearrangement product **120**, which upon deprotection affords the thiophenols **121**.
15 Preferably, 2-methylthiophenol **123** is protected by conversion to the benzoyl derivative **124**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **125**. This material is reacted with a sodium dialkyl phosphite **119**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **126**. Alternatively,
20 the bromomethyl compound **125** can be converted into the phosphonate **126** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **125** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100° to produce the phosphonate **126**. Deprotection of **126**, for example by treatment with aqueous ammonia, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the
25 thiol **127**.
Using the above procedures, but employing, in place of the bromomethyl compound **125**, different bromomethyl compounds **118**, there are obtained the corresponding thiols **121**.

Scheme 23 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **128** is reacted with a dialkyl hydroxyalkylphosphonate **129** under the conditions of the Mitsunobu reaction, for example as described in Org. React., 1992, 42,

335, to afford the coupled product 130. Deprotection then yields the O- or S-linked products 131.

Preferably, the substrate, for example 3-hydroxythiophenol, 132, is converted into the monotrityl ether 133, by reaction with one equivalent of trityl chloride, as described above.

5 This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate 134 in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound 135. Removal of the trityl protecting group, as described above, then affords the thiophenol 136.

Using the above procedures, but employing, in place of the phenol 132, different phenols or
10 thiophenols 128, there are obtained the corresponding thiols 131.

Scheme 24 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol 137 is reacted with an activated ester, for example the trifluoromethanesulfonate, of a dialkyl hydroxyalkyl phosphonate 138, to afford the coupled
15 product 139. Deprotection then affords the thiol 140.

For example, the substrate, 4-methylaminothiophenol 141, is reacted with one equivalent of acetyl chloride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the product 142. This material is then reacted with, for example, diethyl trifluoromethanesulfonylmethyl phosphonate 143, the preparation of
20 which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product 144.

Preferably, equimolar amounts of the phosphonate 143 and the amine 142 are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product 144. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Amer.
25 Chem. Soc., 85, 1337, 1963, then affords the thiophenol 145.

Using the above procedures, but employing, in place of the thioamine 142, different phenols, thiophenols or amines 137, and/or different phosphonates 138, there are obtained the corresponding products 140.

Scheme 25 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate 146.

In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol 137 is
5 reacted with a dialkyl bromoalkyl phosphonate 146 to afford the product 147. Deprotection then affords the free thiophenol 148.

For example, 3-hydroxythiophenol 149 is converted into the S-trityl compound 150, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate 151, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction
10 is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°, to yield the ether product 152. Deprotection, as described above, then affords the thiol 153.

15 Using the above procedures, but employing, in place of the phenol 149, different phenols, thiophenols or amines 137, and/or different phosphonates 146, there are obtained the corresponding products 148.

Scheme 26 depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by
20 means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 155 is coupled with an aromatic bromo compound 154. In this procedure, a suitably protected bromo-substituted thiophenol 154 is reacted with a terminally unsaturated phosphonate 155, to afford the coupled product 156. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate 157, or the
25 saturated analog 159.

For example, 3-bromothiophenol is converted into the S-Fm derivative 160, as described above, and this compound is reacted with diethyl 1-butenyl phosphonate 161, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med.
30 Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for

example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product 162. Deprotection, as described above, then affords the thiol 163.

Optionally, the initially formed unsaturated phosphonate 162 can be subjected to catalytic hydrogenation, using, for example, palladium on carbon as catalyst, to yield the saturated product 164, which upon deprotection affords the thiol 165.

Using the above procedures, but employing, in place of the bromo compound 160, different bromo compounds 154, and/or different phosphonates 155, there are obtained the corresponding products 157 and 159.

- 10 Scheme 28 illustrates the preparation of an aryl-linked phosphonate ester 169 by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57.

- 15 The sulfur-substituted phenylboronic acid 166 is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product 168 which is deprotected to yield the thiol 169.

- For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in
20 Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate 170. This material is reacted with diethyl 4-bromophenylphosphonate 171, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium
25 (0) and an inorganic base such as sodium carbonate, to afford the coupled product 172. Deprotection, for example by the use of tetrabutyl ammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol 173.

Using the above procedures, but employing, in place of the boronate 170, different boronates 166, and/or different phosphonates 167, there are obtained the corresponding products 169.

Scheme 29 depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring.

In this procedure, a suitably protected O, S or N-substituted thiophenol 137 is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate 174, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product 175 is then deprotected to afford the thiol 176. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester 177 by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol 177 is then reacted with, for example diethyl 4-(bromomethyl)phenylphosphonate, 178, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The thioether product 179 thus obtained is deprotected, as described above, to afford the thiol 180.

Using the above procedures, but employing, in place of the thiophenol 177, different phenols, thiophenols or amines 137, and/or different phosphonates 174, there are obtained the corresponding products 176.

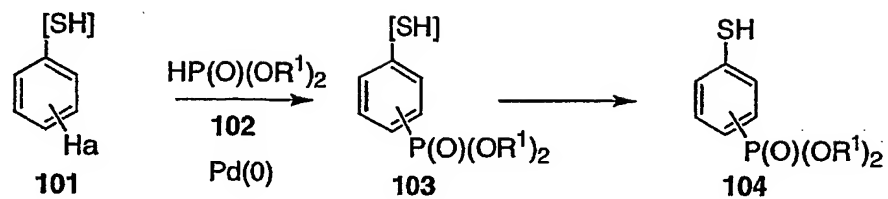
Scheme 30 illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol 181, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is $CH=CH$) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate 138, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester 182. Deprotection, as described above, then affords the thiol 183. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in

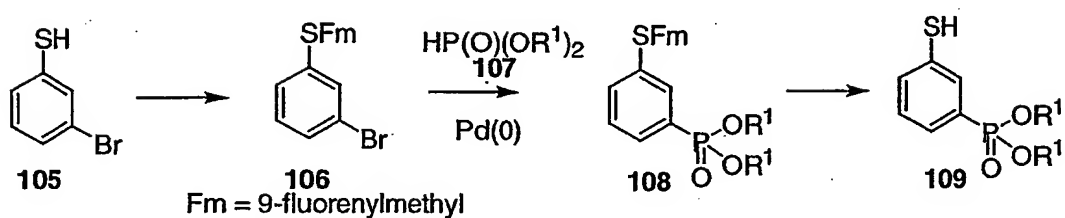
J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al., eds., Pergamon, 1995, Vol. 2, p. 707. For example, 2,3-dihydro-1H-indole-5-thiol, **184**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **185**, as described above, and the ester is then reacted with the triflate **143**, using the conditions described above for the preparation of **144**, (Scheme 24), to yield the phosphonate **186**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **187**. Using the above procedures, but employing, in place of the thiol **184**, different thiols **181**, and/or different triflates **138**, there are obtained the corresponding products **183**.

Scheme 20

Method

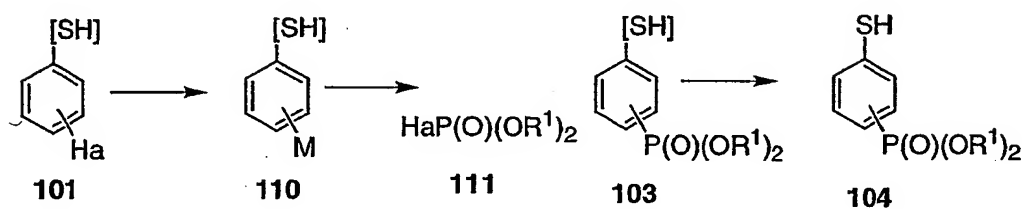


Example

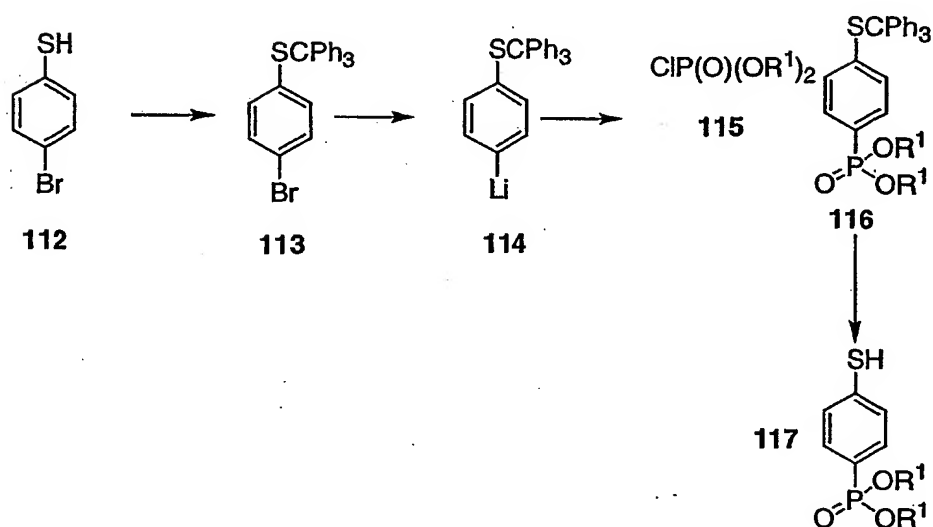


Scheme 21

Method

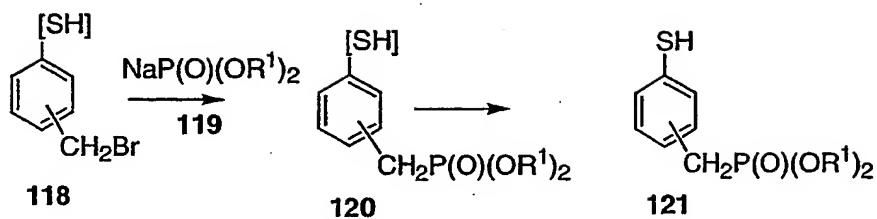


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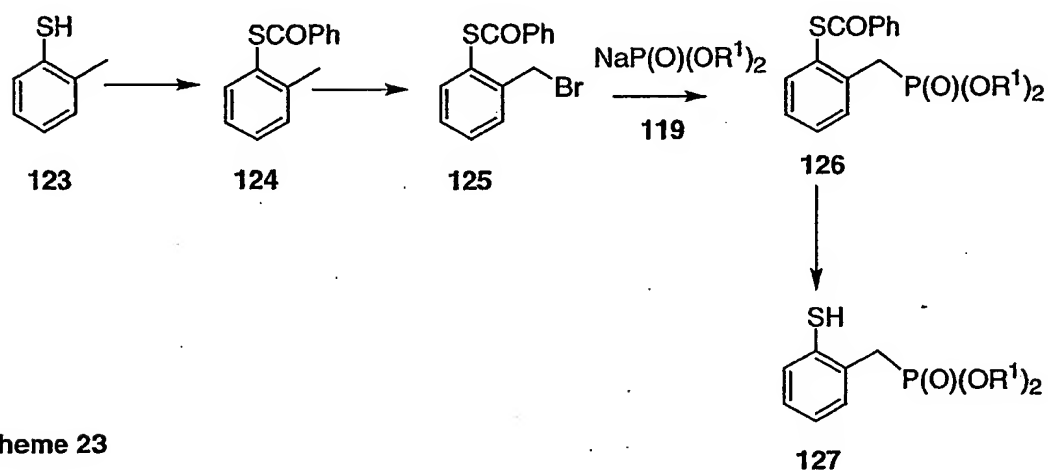


Scheme 22

Method

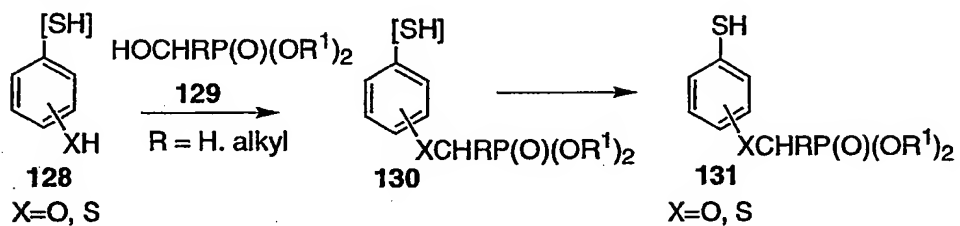


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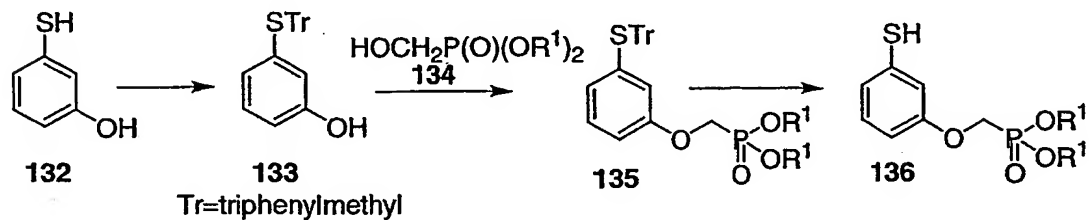


Scheme 23

Method

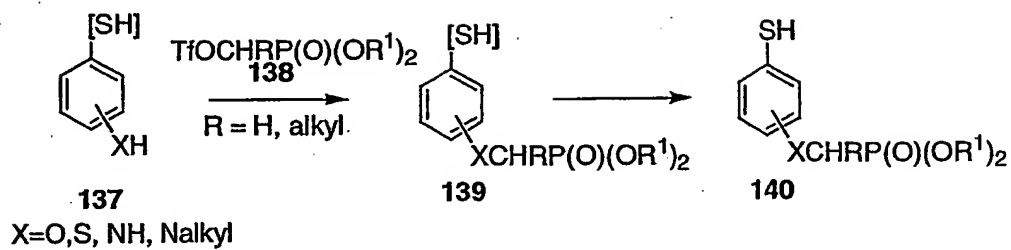


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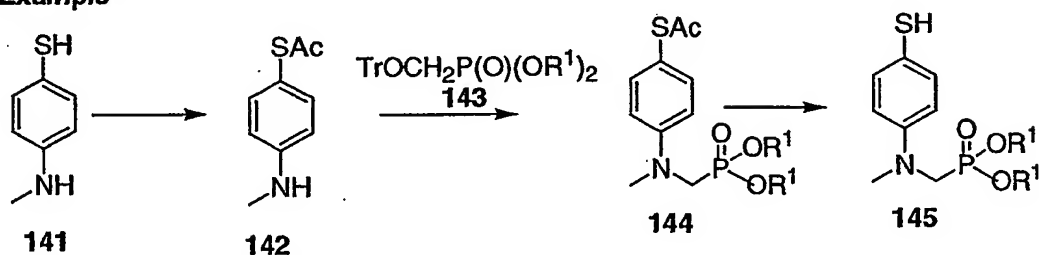


Scheme 24

Method

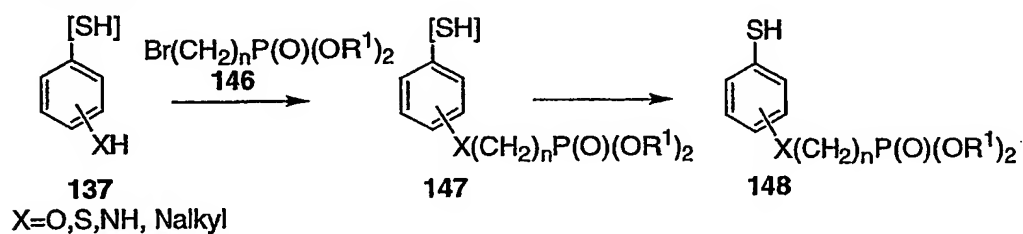


Example

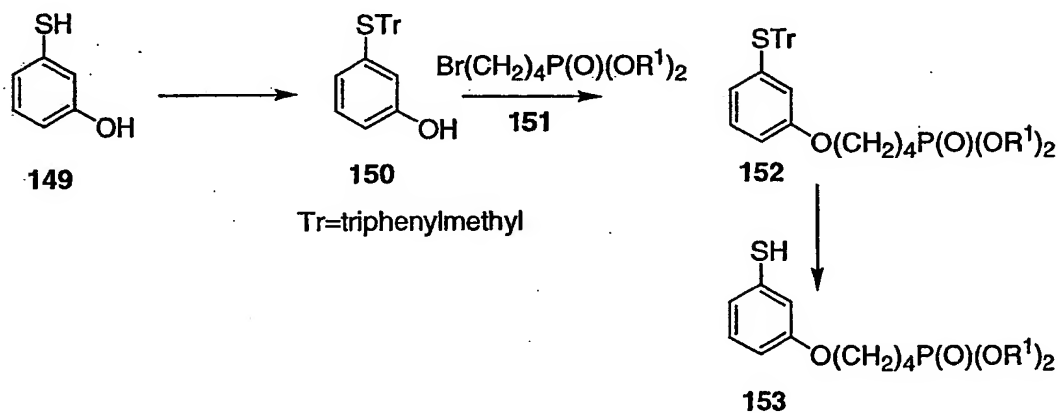


Scheme 25

Method

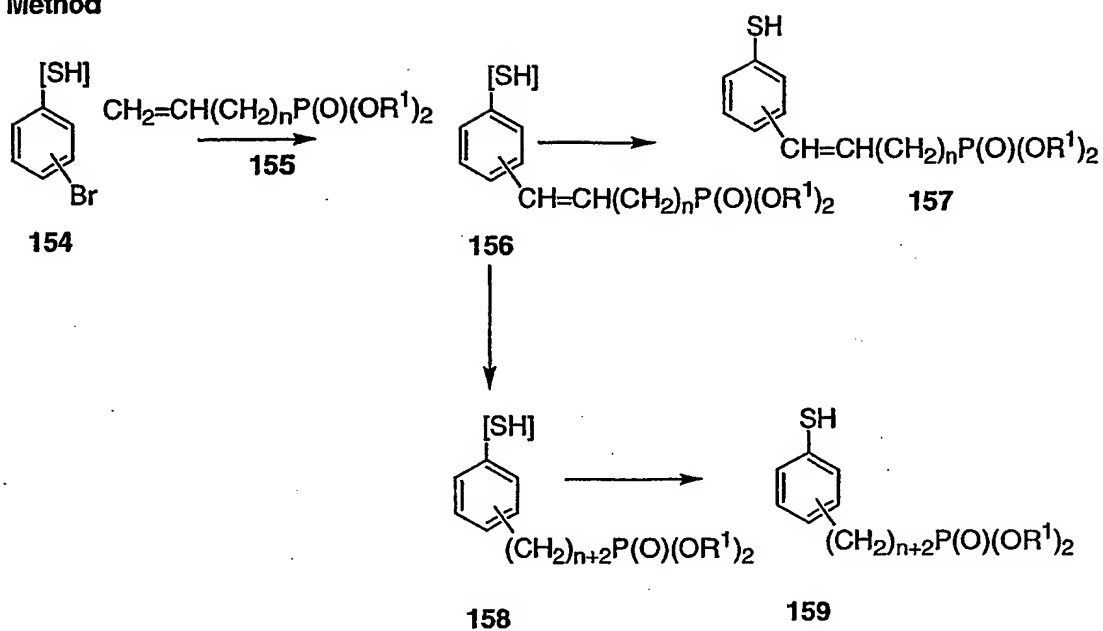


Example

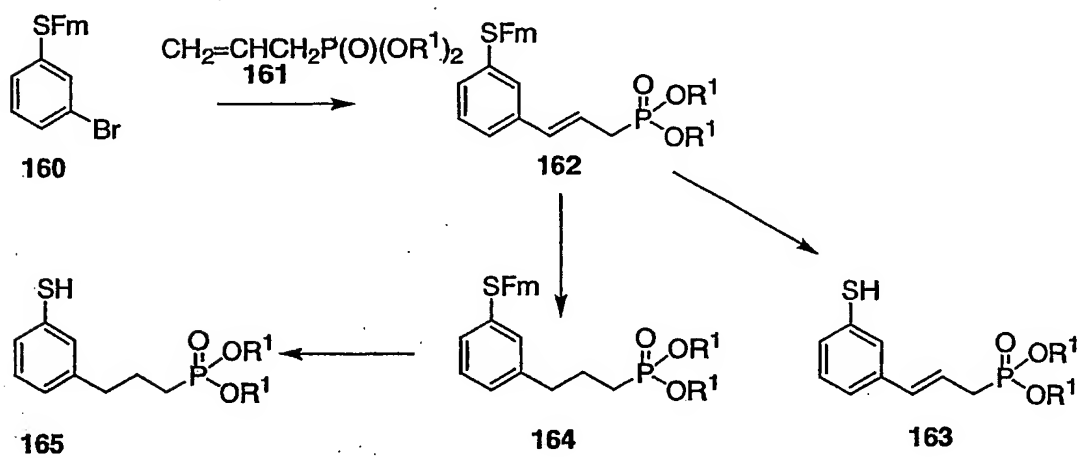


Scheme 26

Method

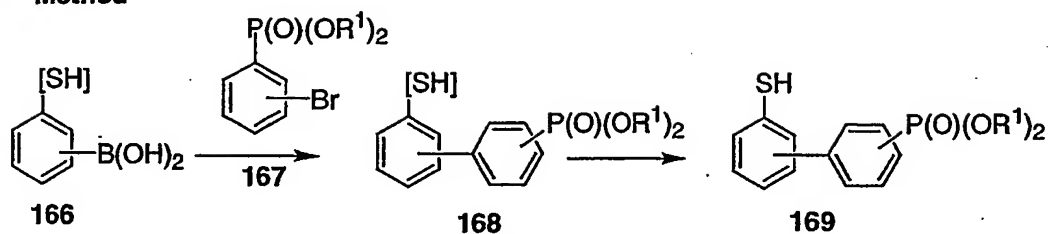


Example

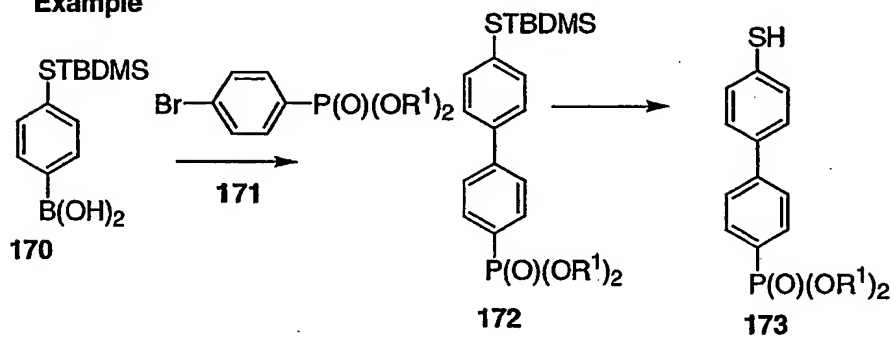


Scheme 28

Method

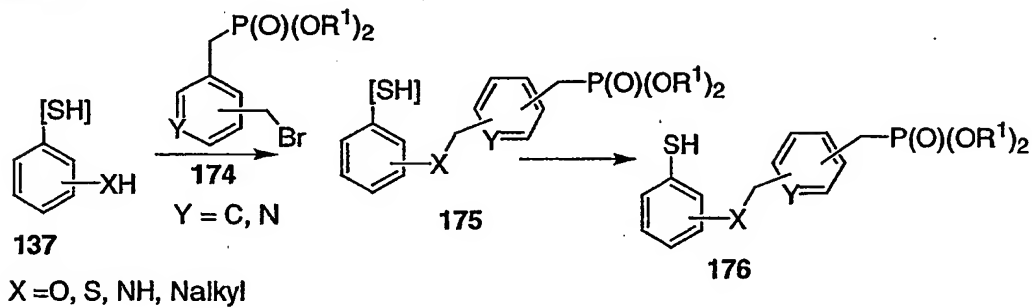


Example

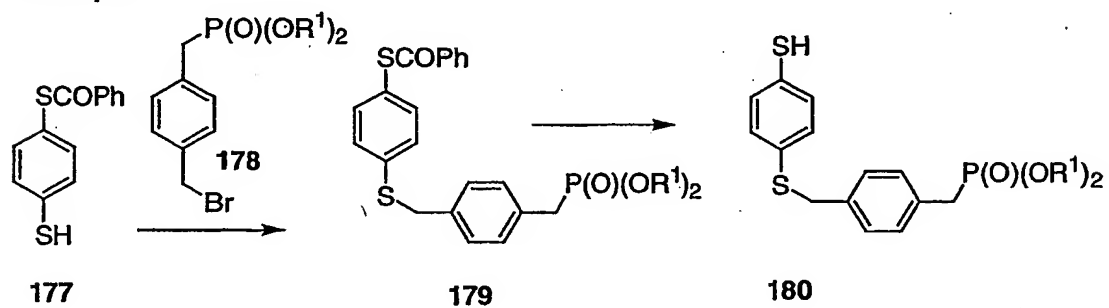


Scheme 29

Method

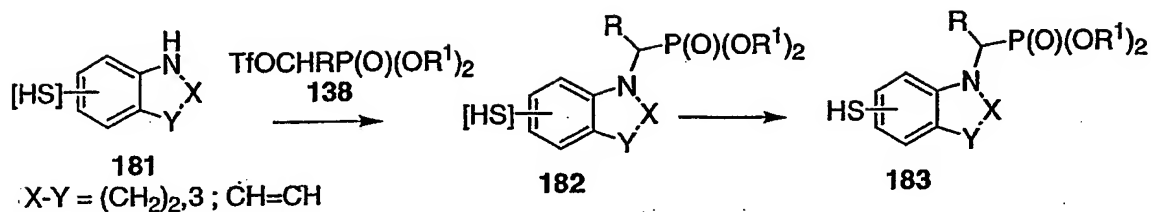


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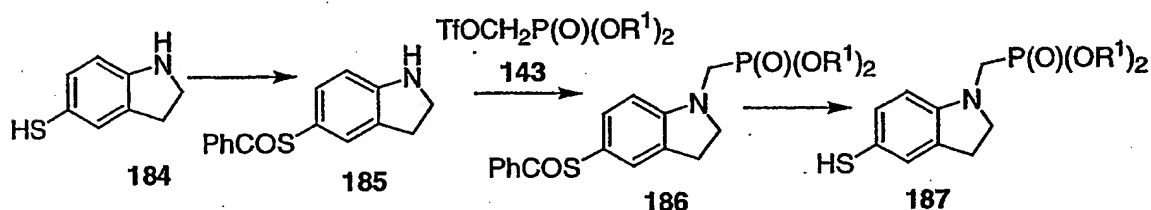


Scheme 30

Method



Example



Preparation of benzoic acid derivatives incorporating phosphonate moieties.

Scheme 31 illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid **188** is subjected to halogen-methyl exchange to afford the organometallic intermediate **189**. This compound is reacted with a chlorodialkyl phosphite **115** to yield the phenylphosphonate ester **190**, which upon deprotection affords the carboxylic acid **191**.

- For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, **192**, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Amer. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **193**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester **194**. This compound is treated with boron trifluoride at 0° to effect rearrangement to the orthoester **195**, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether **196**. Halogen-metal exchange is performed by the reaction of **196** with butyllithium, and the lithiated intermediate is then coupled with a

chlorodialkyl phosphite 115, to produce the phosphonate 197. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid 198.

- 5 Using the above procedures, but employing, in place of the bromo compound 192, different bromo compounds 188, there are obtained the corresponding products 191.

Scheme 32 illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

- 10 In this method, a suitably protected dimethyl hydroxybenzoic acid, 199, is reacted with a brominating agent, so as to effect benzylic bromination. The product 200 is reacted with a sodium dialkyl phosphite, 119, to effect displacement of the benzylic bromide to afford the phosphonate 201.

- For example, 2,5-dimethyl-3-hydroxybenzoic acid, 203, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p. 17, to afford the ether ester 204. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or diisopropylethylamine. The product 204 is then reacted with a brominating agent, for example
- 20 N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product 205. This compound is then reacted with a sodium dialkyl phosphite 119, using the conditions described above for the preparation of 120, (Scheme 22) to afford the phosphonate 206. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields
- 25 the carboxylic acid 207.

Using the above procedures, but employing, in place of the methyl compound 203, different methyl compounds 199, there are obtained the corresponding products 202.

- Scheme 33 illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom.
- 30

In this method, a suitably protected hydroxy- or mercapto-substituted hydroxymethyl benzoic acid 208 is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl

hydroxymethyl phosphonate 134, to afford the coupled product 209, which upon deprotection affords the carboxylic acid 210.

For example, 3,6-dihydroxy-2-methylbenzoic acid, 211, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester 212, by
5 treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, using the conditions described above for the preparation of 170, to afford the mono-silyl ether 213. This compound is then reacted with a dialkyl hydroxymethylphosphonate 134, under the
10 conditions of the Mitsunobu reaction, as described above for the preparation of 130, (Scheme 23) to afford the coupled product 214. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic carboxylic acid 215.

Using the above procedures, but employing, in place of the phenol 211, different phenols or
15 thiophenols 208, there are obtained the corresponding products 210.

Scheme 34 depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains.

In this method, a dialkyl alkenylphosphonate 216 is coupled, by means of a palladium
20 catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid 217. The product 218 can be deprotected to afford the phosphonate 219, or subjected to catalytic hydrogenation to afford the saturated compound, which upon deprotection affords the corresponding carboxylic acid 220.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid 221, prepared as described in
25 WO 9218490, is converted as described above, into the silyl ether OBO ester 222. This compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate 223, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above for the preparation of 156, (Scheme 26) to afford the product 224.

Deprotection, or hydrogenation/deprotection, of this compound, as described above, then
30 affords respectively the unsaturated and saturated products 225 and 227.

Using the above procedures, but employing, in place of the bromo compound 221, different bromo compounds 217, and/or different phosphonates 216, there are obtained the corresponding products 219 and 220.

- 5 Scheme 35 illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid 217 is converted to the corresponding boronic acid, as described above, (Scheme 28). The product is subjected to a Suzuki coupling reaction, as described above, with a dialkyl bromophenyl
10 phosphonate 229. The product 230 is then deprotected to afford the diaryl phosphonate product 231.

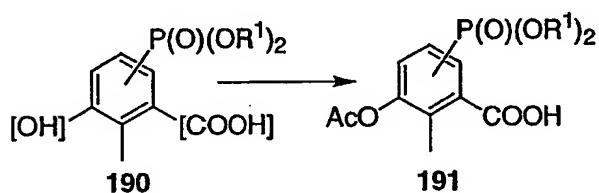
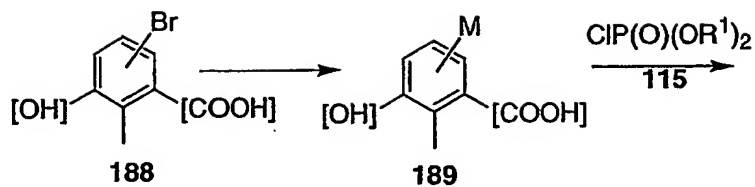
For example, the silylated OBO ester 232, prepared as described above, (Scheme 31), is converted into the boronic acid 233, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate 234, prepared as described in J. Chem. Soc. Perkin
15 Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, as described above for the preparation of 172, (Scheme 28) to afford the diaryl phosphonate 235.

Deprotection, as described above, then affords the benzoic acid 236.

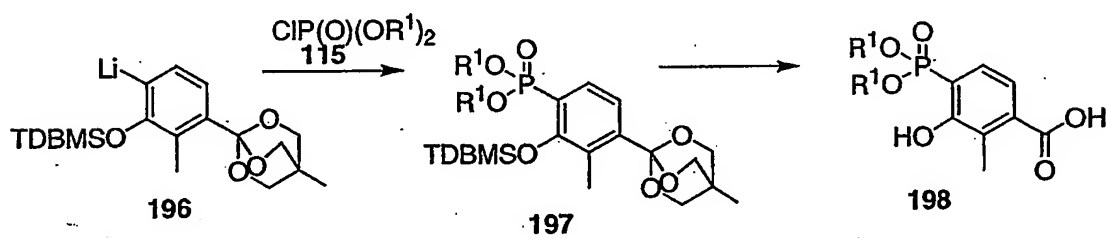
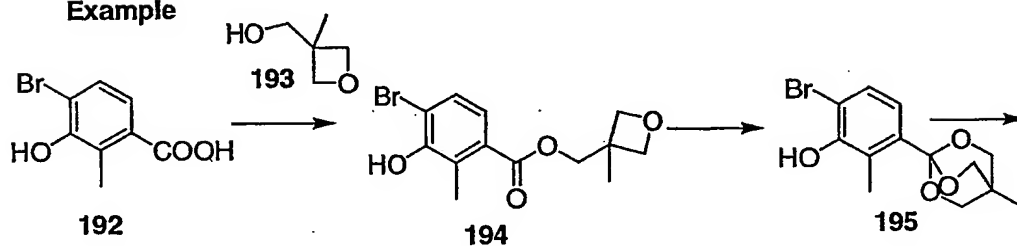
Using the above procedures, but employing, in place of the bromo compound 232, different bromo compounds 217, and/or different phosphonates 229, there are obtained the
20 corresponding carboxylic acid products 231.

Scheme 31

Method

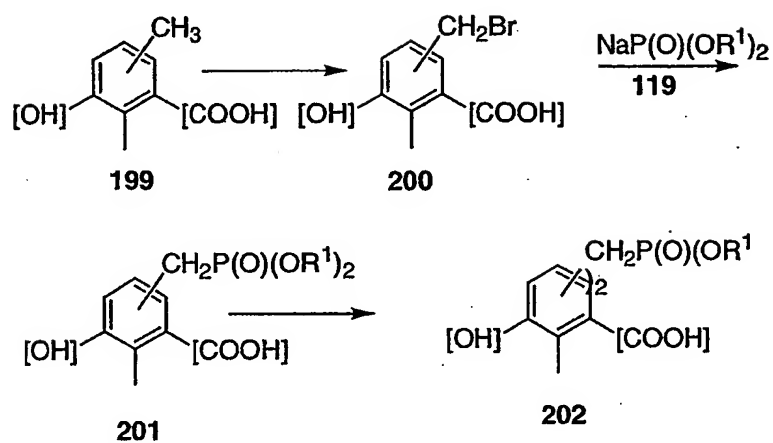


Example

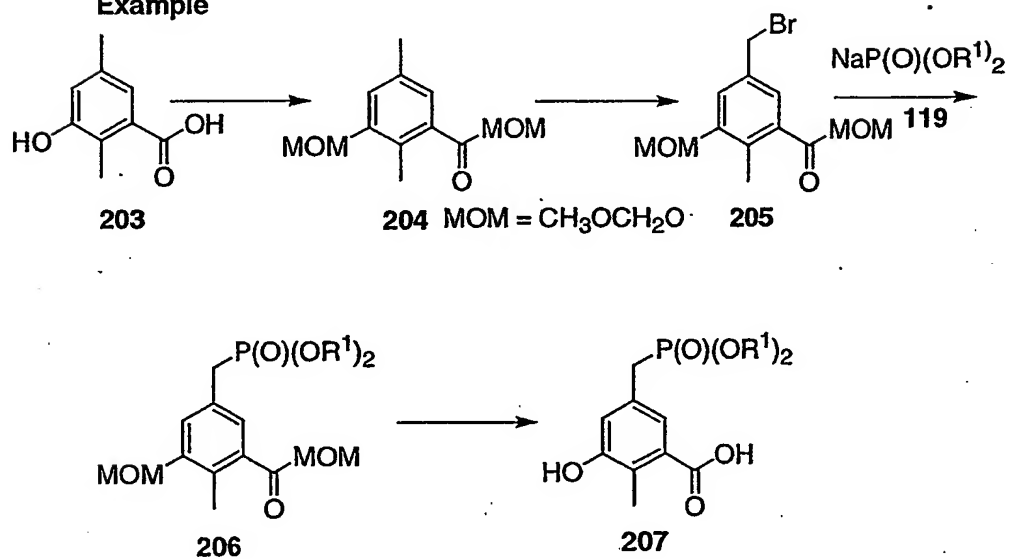


Scheme 32

Method

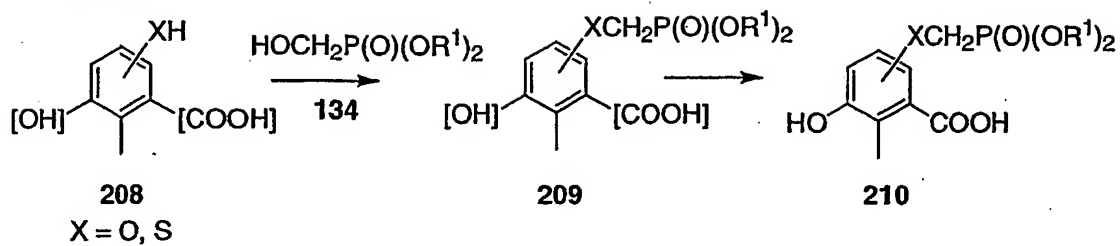


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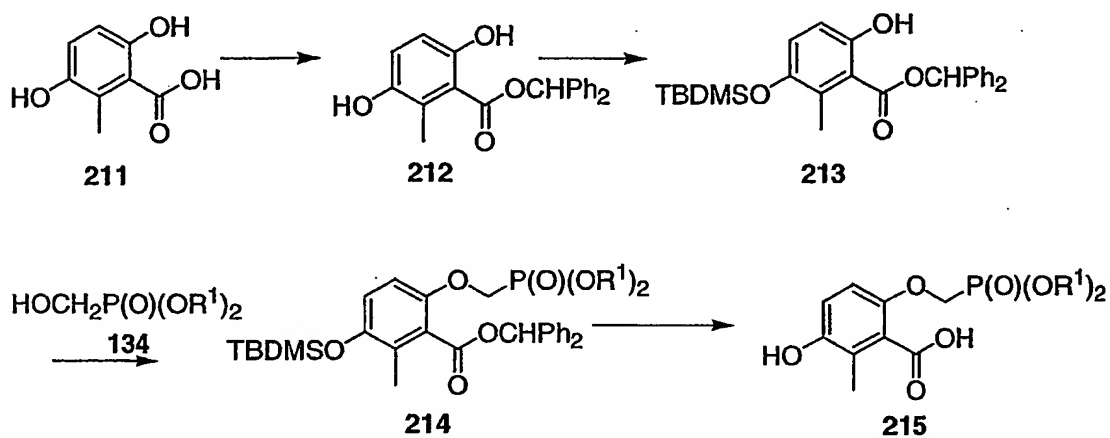


Scheme 33

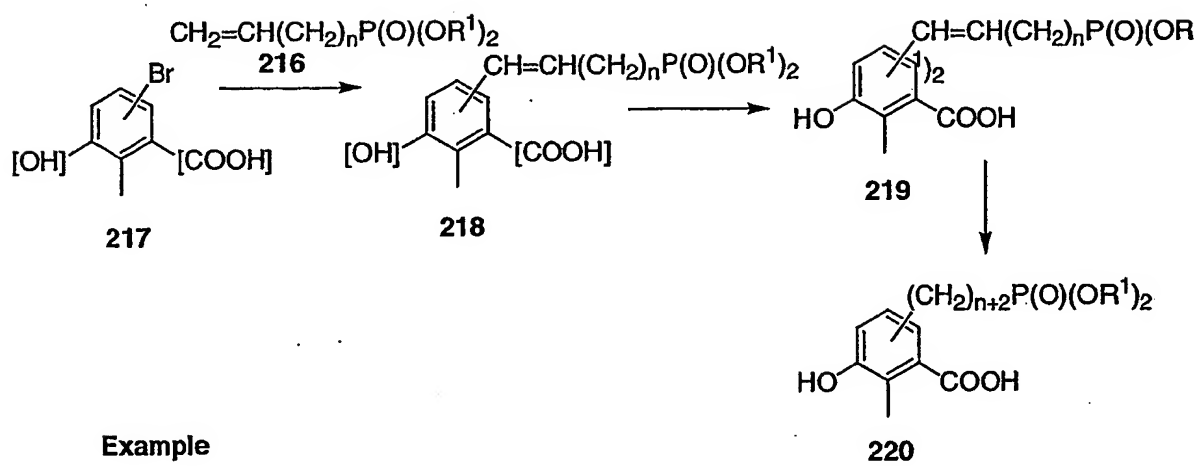
Method



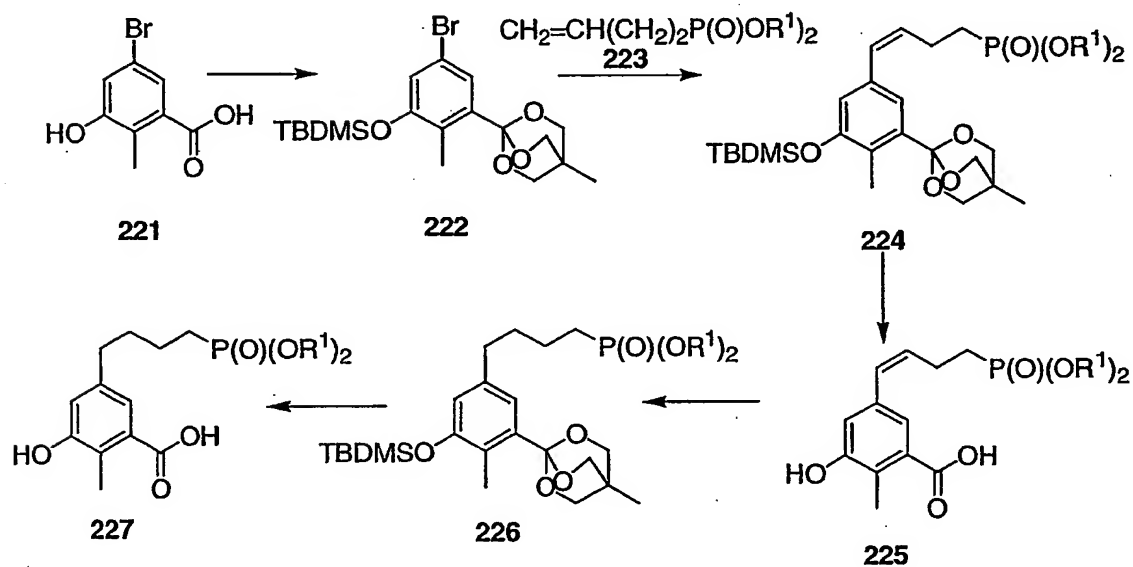
Example



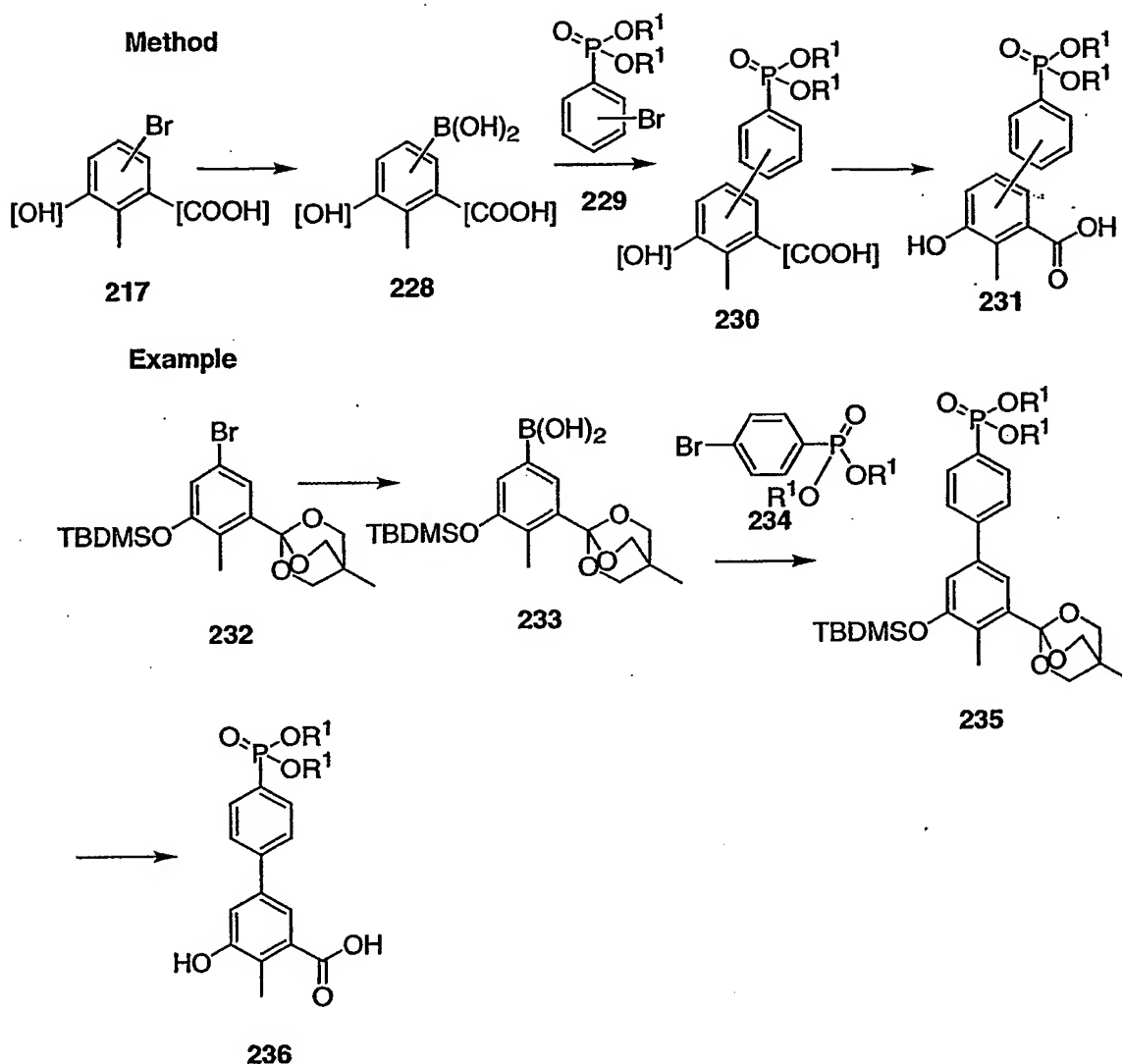
Scheme 34
Method



Example



Scheme 35



Preparation of tert-butylamine derivatives incorporating phosphonate moieties.

- Scheme 36 describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2,2-dimethyl-2-aminoethylbromide **237** is reacted with a trialkyl phosphite, under the conditions of the Arbuzov reaction, as described above, to afford the phosphonate **238**.

For example, the cbz derivative of 2,2-dimethyl-2-aminoethylbromide **240**, is heated with a trialkyl phosphite at ca 150° to afford the product **241**. Deprotection, as previously described, then affords the free amine **242**.

- Using the above procedures, but employing different trisubstituted phosphites, there are
5 obtained the corresponding amines **239**.

Scheme 37 illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain.

- An optionally protected alcohol or thiol **243** is reacted with a bromoalkylphosphonate **146**, to
10 afford the displacement product **244**. Deprotection, if needed, then yields the amine **245**.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol **246** is reacted with a dialkyl 4-bromobutyl phosphonate **247**, prepared as described in Synthesis, 1994, 9, 909, in dimethylformamide containing potassium carbonate and potassium iodide, at ca 60° to afford the phosphonate **248**. Deprotection then affords the free amine **249**.

- 15 Using the above procedures, but employing different alcohols or thiols **243**, and/or different bromoalkylphosphonates **146**, there are obtained the corresponding products **245**.

Scheme 38 describes the preparation of carbon-linked phosphonate tert butylamine derivatives, in which the carbon chain can be unsaturated or saturated.

- 20 In the procedure, a terminal acetylenic derivative of tert-butylamine **250** is reacted, under basic conditions, with a dialkyl chlorophosphite **115**, as described above in the preparation of **104**, (Scheme 21). The coupled product **251** is deprotected to afford the amine **252**. Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products **253** and **254** respectively.

- 25 For example, 2-amino-2-methylprop-1-yne **255**, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative **256**, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide in tetrahydrofuran at -78°. The resultant anion is then reacted with a dialkyl chlorophosphite
30 **115** to afford the phosphonate **257**. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine **258**. Partial catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for

Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p. 566, produces the olefinic phosphonate **259**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **260**.

- 5 Using the above procedures, but employing different acetylenic amines **250**, there are obtained the corresponding products **252**, **253** and **254**.

Scheme 39 illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

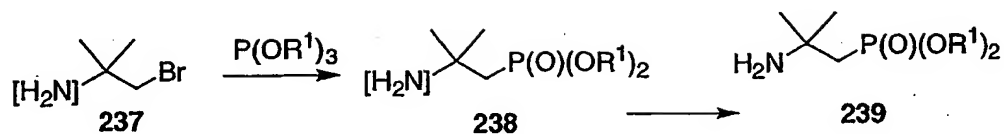
- 10 In this method, an aminoethyl-substituted cyclic amine **261** is reacted with a limited amount of a bromoalkyl phosphonate **146**, using, for example, the conditions described above for the preparation of **147**, (Scheme 25) to afford the displacement product **262**.

For example, 3-(1-amino-1-methyl)ethylpyrrolidine **263**, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with a dialkyl 4-bromobutyl phosphonate

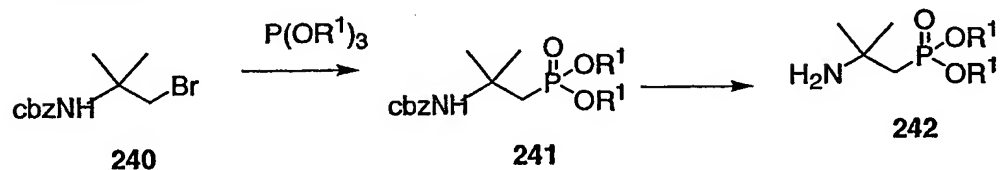
- 15 **151**, prepared as described in Synthesis, 1994, 9, 909, to afford the displacement product **264**.
Using the above procedures, but employing different cyclic amines **261**, and/or different bromoalkylphosphonates **146**, there are obtained the corresponding products **262**.

Scheme 36

Method

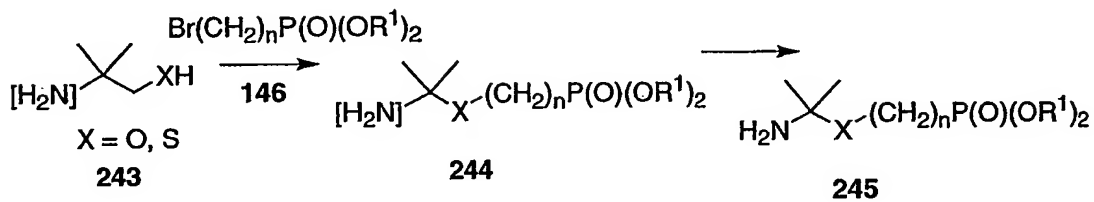


Example

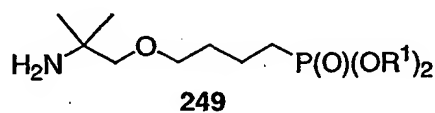
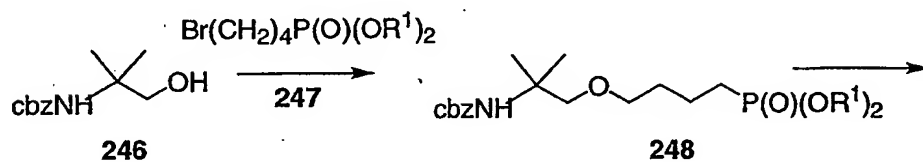


Scheme 37

Method

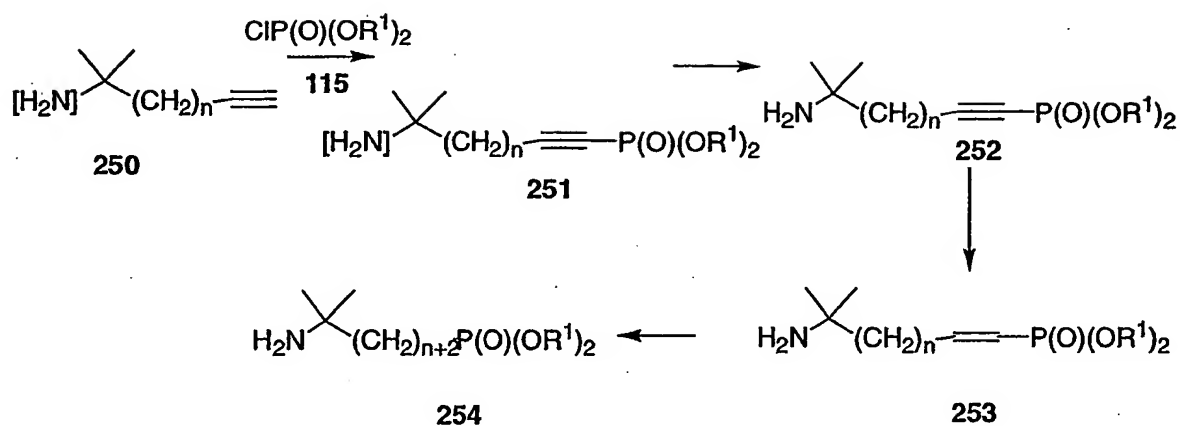


Example

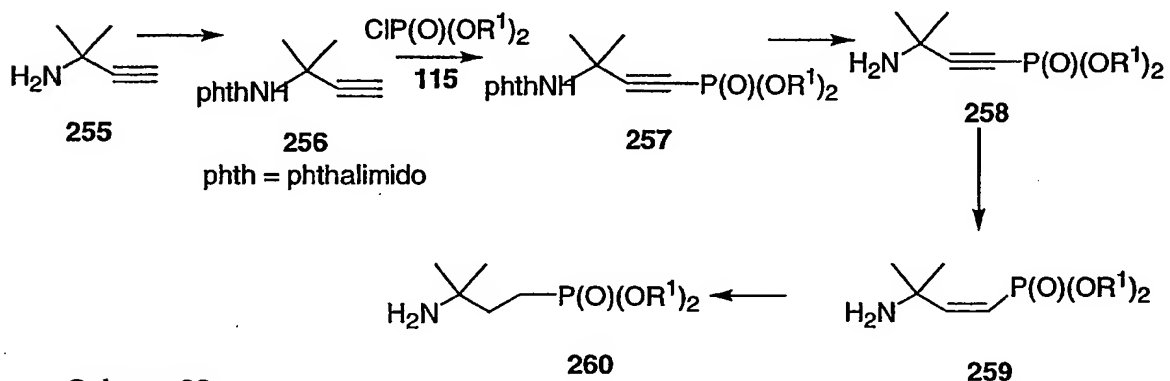


Scheme 38

Method

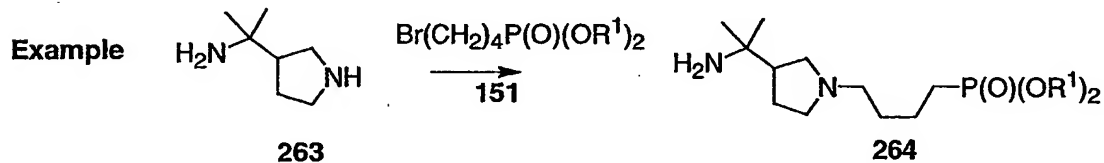
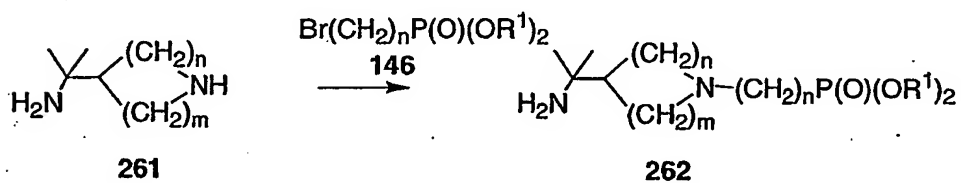


Example



Scheme 39

Method



Preparation of decahydroquinolines with phosphonate moieties at the 6-position.

Chart 6 illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the intermediate 265 are shown.

In the first route, 2-hydroxy-6-methylphenylalanine 266, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative 267. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product 267, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product 268. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound 268 is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline 265, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline 265 can be obtained from 2-hydroxyphenylalanine 269, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem. Rev., 1995, 95, 1797.

Typically, the substrate 269 is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product 265, in which R is H.

Catalytic hydrogenation of the latter compound, using, for example, platinum as catalyst, as described in J. Amer. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-substituted decahydroisoquinoline 270. The reduction can also be performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline 265 is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°, to afford the decahydroisoquinoline 270.

Protection of the carboxyl and NH groups present in 270 for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example, pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone 276, in which R is trichloroethyl and R₁ is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Amer. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butyl aluminum hydride, as described in J. Amer. Chem. Soc., 80, 5372, 1958, then affords the alcohol 277.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as, for example, isopropanol, at ambient temperature, to afford the alcohol 277. The alcohol 270 carboxyl and NH groups can be protected, for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and by conversion of the NH into the N-cbz group, as described above. The protected alcohol 270 can then be converted into the thiol 271 and the amine 272, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry. For example, the alcohol 270 can be converted into an activated ester, for example trifluoromethanesulfonyl ester or the methanesulfonate ester 273, by treatment with methanesulfonyl chloride, as described above for the preparation of 63, (Scheme 1). The mesylate 273 is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol 271.

For example, the mesylate 273 is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate 274, in which R₂ is COCH₃. The product then treated with, a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol 271.

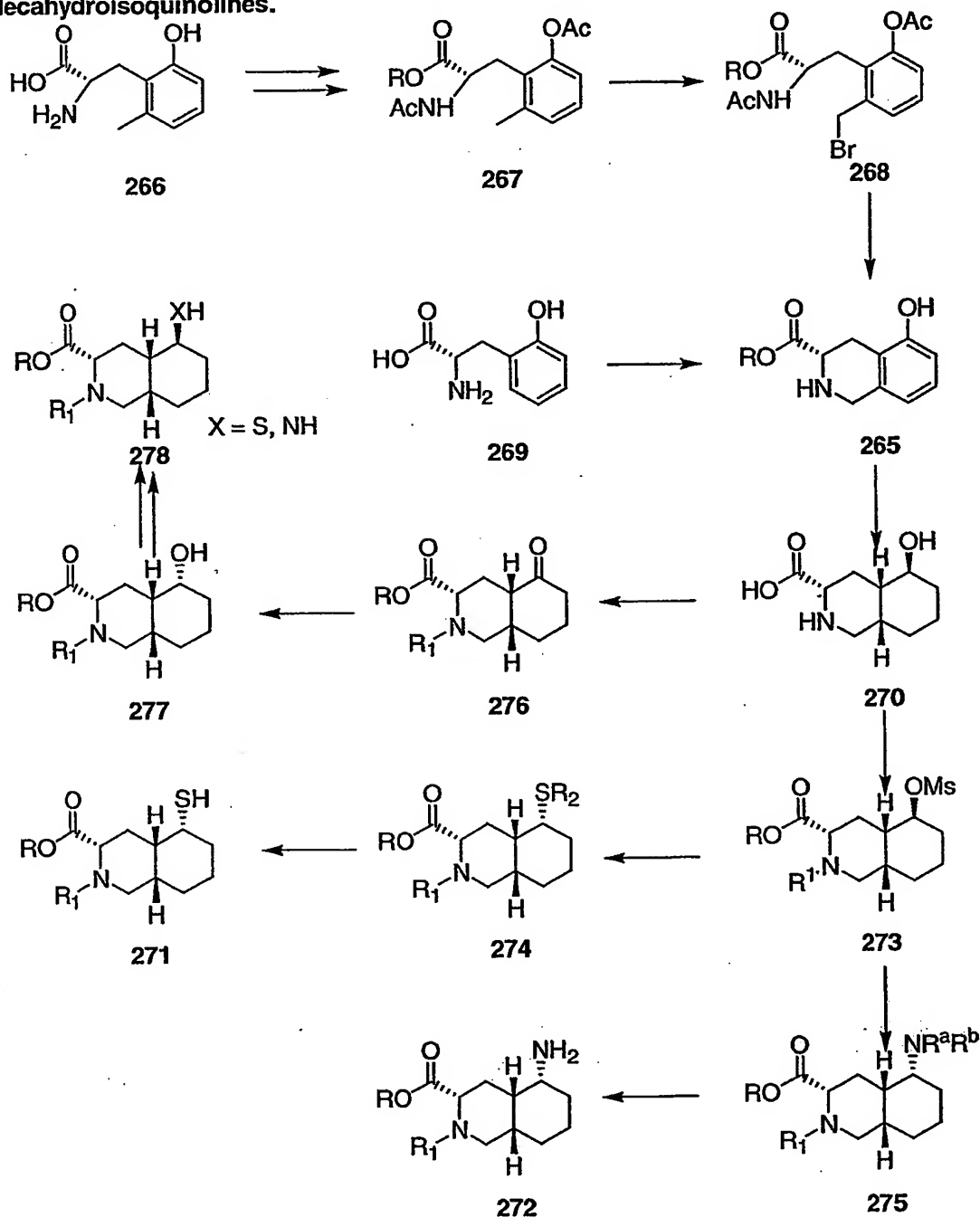
The mesylate 273 can be treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p. 399, to afford the amine 272.

For example, the mesylate **273** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **275**, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example
5 by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine **272**.

The application of the procedures described above for the conversion of the β -carbinol **270** to the α -thiol **271** and the α -amine **272** can also be applied to the α -carbinol **277**, so as to afford the β -thiol and β -amine, **278**.

10

Chart 6. Intermediates for the preparation of phosphonate-containing decahydroisoquinolines.



Scheme 40 illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain.

In this procedure, an alcohol, thiol or amine 279 is reacted with a bromoalkyl phosphonate

5 146, under the conditions described above for the preparation of 147 (Scheme 25), to afford

the displacement product **280**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **281**.

For example, the compound **282**, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, **283**, the preparation of which is described in J. Amer. Chem. Soc., 2000, 122, 1554 to afford the displacement product **284**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **285**.

Using the above procedures, but employing, in place of the α -thiol **282**, the alcohols, thiols or amines **270**, **272**, **277**, and **278**, of either α - or β -orientation, there are obtained the corresponding products **281**, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme 41 illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p. 421.

In this procedure, the amines **272** or **278** are reacted with a phosphonate aldehyde **286**, in the presence of a reducing agent, to afford the alkylated amine **287**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **288**.

For example, the protected amino compound **272** is reacted with a dialkyl formylphosphonate **289**, the preparation of which is described in U.S. Patent 3,784,590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **290**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **291**.

Using the above procedures, but employing, instead of the α -amine **272**, the β isomer, **278** and/or different aldehydes **286**, there are obtained the corresponding products **288**, in which the orientation of the side chain is the same as that of the amine precursor.

Scheme 42 depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.

In this procedure, a thiol phosphonate 292 is reacted with a mesylate 293, to effect

- 5 displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product 294. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine 295. For example, the protected mesylate 273 is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate 296, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thio ether phosphonate 297. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine 298.
- 15 Using the above procedures, but employing, instead of the phosphonate 296, different phosphonates 292, there are obtained the corresponding products 295.

- Scheme 43 illustrates the preparation of decahydroisoquinoline phosphonates 299 in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates 300 and a bromomethyl substituted phosphonate 301. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant 300. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate can be employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is required. The displacement reaction affords the ether, thioether or amine compounds 302. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine 299.
- 20

- For example, the protected alcohol 303 is reacted at ambient temperature with a dialkyl 3-bromomethyl phenylmethylphosphonate 304, the preparation of which is described above, (Scheme 29). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a
- 30

strong base, such as, for example, lithium hexamethyldisylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate **304**, to afford the product **305**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **306**.

- 5 Using the above procedures, but employing, instead of the β -carbinol **303**, different carbinols, thiols or amines **300**, of either α - or β -orientation, and/or different phosphonates **301**, in place of the phosphonate **304**, there are obtained the corresponding products **299**, in which the orientation of the side-chain is the same as that of the starting material **300**.

- 10 Schemes 43-43 illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme 44 illustrates the conversion of the latter group of compounds **307** (in which the group B is link-P(O)(OR¹)₂ and precursor compounds thereto (in which B is an optionally protected precursor to the group link-P(O)(OR¹)₂ such as, for example, OH, SH, NH₂) to the

- 15 corresponding tert butyl amides **88**.

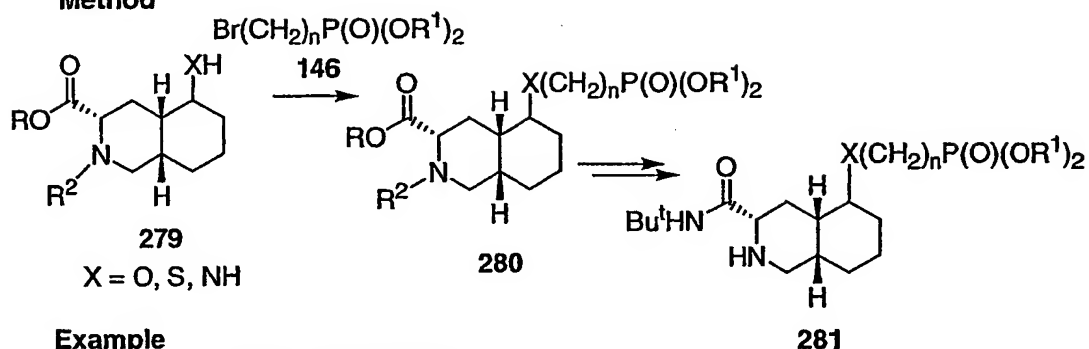
As shown in Scheme 44, the ester compounds **307** are deprotected to form the corresponding carboxylic acids **308**. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R², and the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is

- 20 removed by treatment with zinc in acetic acid, as described in J. Amer. Chem. Soc., 88, 852, 1966. Conversion of the carboxylic acid **308** to the tert. butyl amide **309** is then accomplished by reaction of the carboxylic acid, or an activated derivative thereof, with tert. butylamine, as described above for the preparation of **62** (Scheme 1). Deprotection of the NR² group, as described above, then affords the free amine **88**.

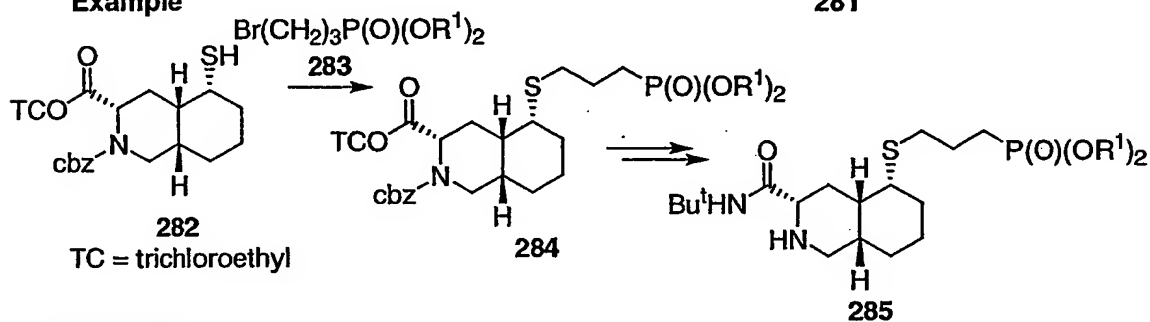
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Scheme 40

Method

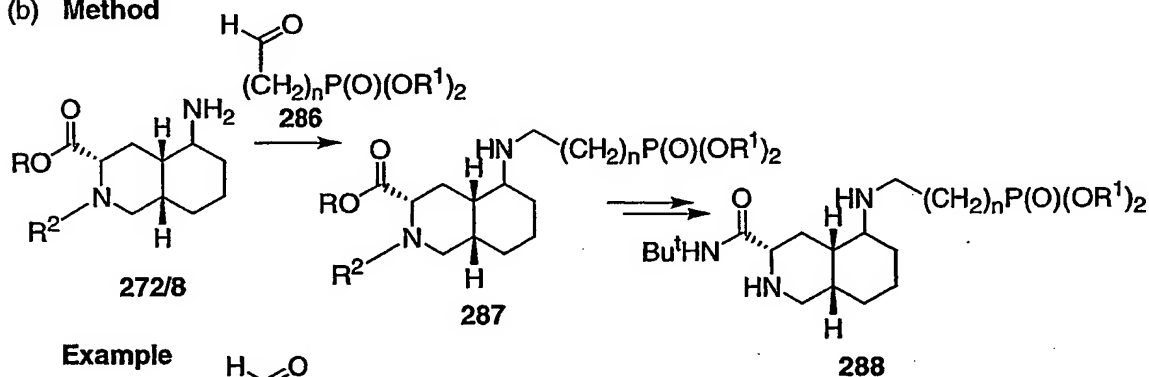


Example

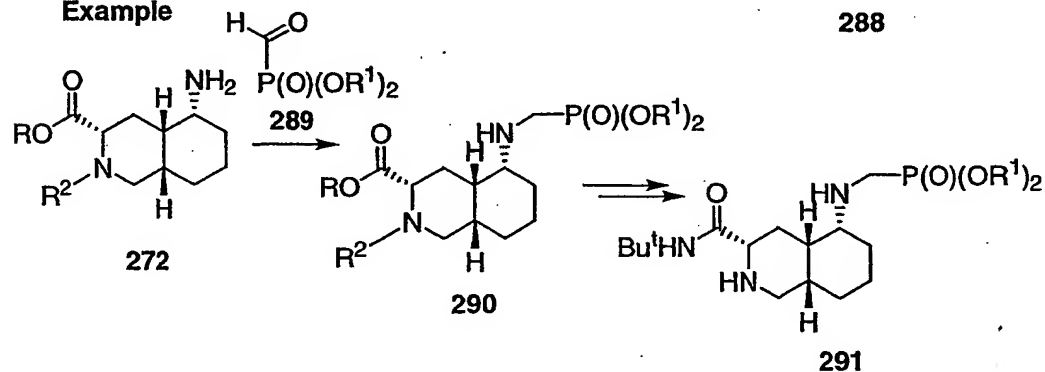


Scheme 41

(b) Method

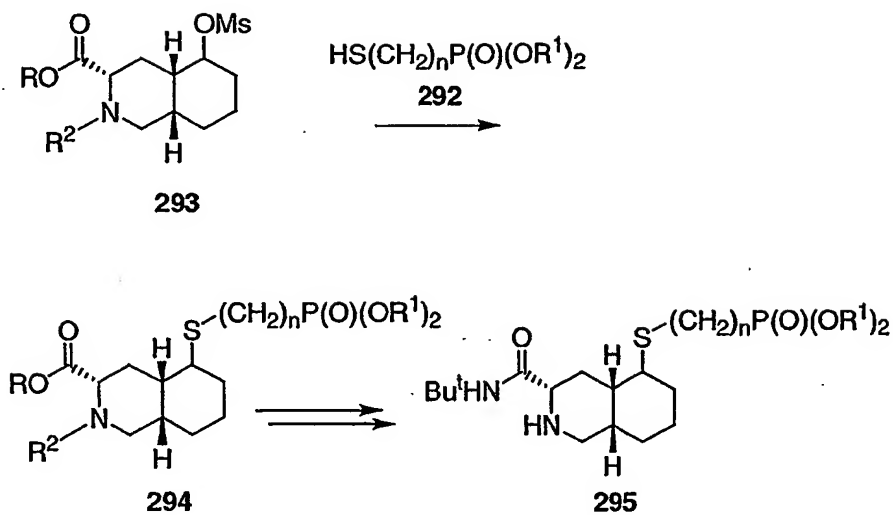


Example

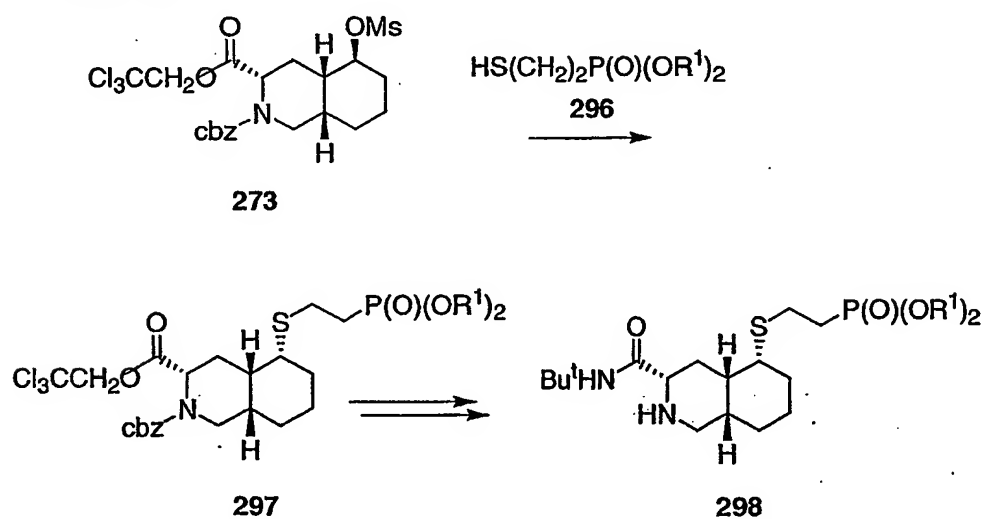


Scheme 42

Method

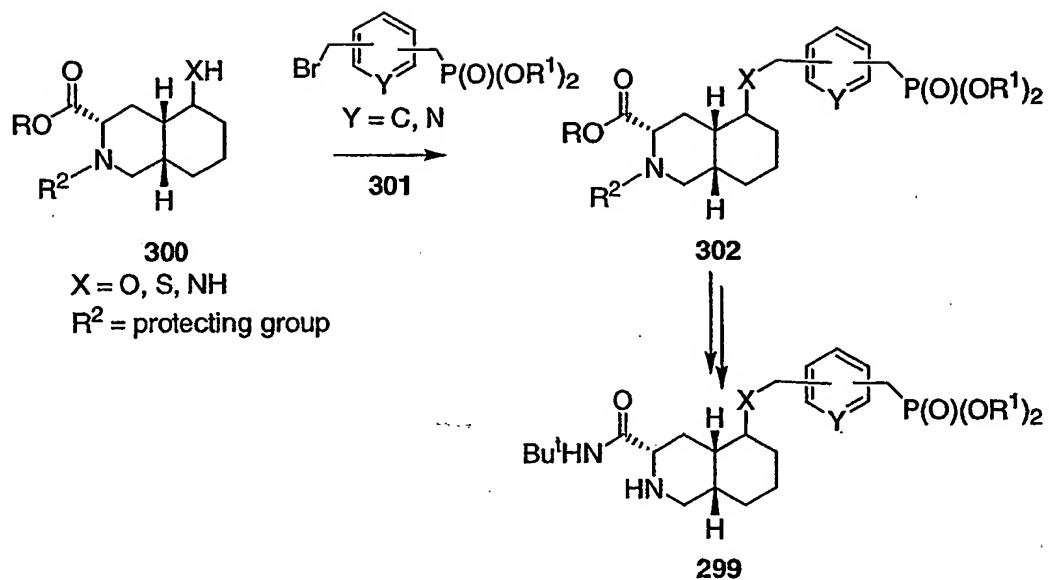


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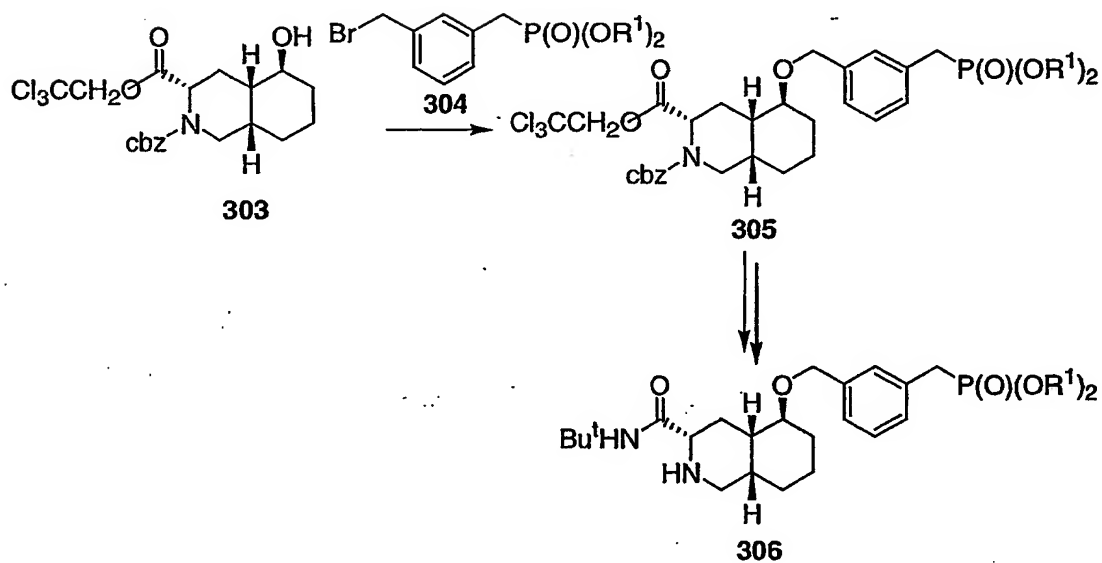


Scheme 43

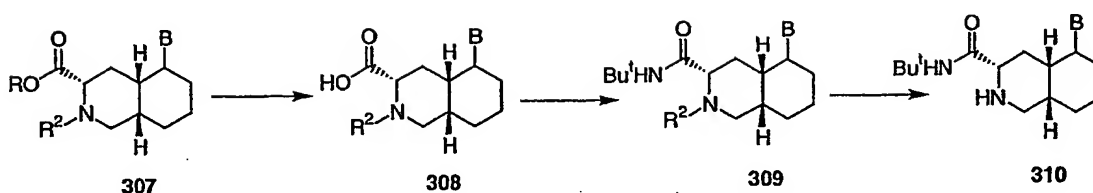
Method



Example



Scheme 44



Preparation of phenylalanine derivatives incorporating phosphonate moieties.

- Scheme 45 illustrates the conversion of variously substituted phenylalanine derivatives 311 into epoxides 14a-1, the incorporation of which into the compounds 2 is depicted in Scheme 14a.
- A number of compounds 311 or 312, for example those in which X is 2, 3, or 4-OH, or X is 4-NH₂ are commercially available. The preparations of different compounds 311 or 312 are described in the literature. For example, the preparation of compounds 311 or 312 in which X is 3-SH, 4-SH, 3-NH₂, 3-CH₂OH or 4-CH₂OH, are described respectively in WO0036136, J. Amer. Chem. Soc., 1997, 119, 7173, Helv. Chim. Acta, 1978, 58, 1465, Acta Chem. Scand., 1977, B31, 109 and Syn. Com., 1998, 28, 4279. Resolution of compounds 311, if required, can be accomplished by conventional methods, for example as described in Recent Dev. Synth. Org. Chem., 1992, 2, 35.
- The variously substituted aminoacids 312 are protected, for example by conversion to the BOC derivative 313, by treatment with BOC anhydride, as described in J. Med. Chem., 1998, 41, 1034. The product 313 is then converted into the methyl ester 314, for example by treatment with ethereal diazomethane. The substituent X in 314 is then transformed, using the methods described below, Schemes 46-48, into the group A. The products 315 are then converted, via the intermediates 316-319, into the epoxides 14a-1. The methyl ester 315 is first hydrolyzed, for example by treatment with one molar equivalent of aqueous methanolic lithium hydroxide, or by enzymatic hydrolysis, using, for example, porcine liver esterase, to afford the carboxylic acid 316. The conversion of the carboxylic acid 316 into the epoxide 14a-1, for example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, is then effected. The carboxylic acid is first converted into the acid chloride, for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone 317. The diazoketone is converted into

the chloroketone **318** by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether. The latter compound is then reduced, for example by the use of sodium borohydride, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer **319** is separated by chromatography. This material is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide **14a-1**. Optionally, the above described series of reactions can be performed on the methyl ester **314**, so as to yield the epoxide **14a-1** in which A is OH, SH, NH, Nalkyl or CH₂OH.

Methods for the transformation of the compounds **314**, in which X is a precursor group to the substituent link-P(O)(OR¹)₂, are illustrated in Schemes 46-48.

Scheme 46 depicts the preparation of epoxides **322** incorporating a phosphonate group linked to the phenyl ring by means of a heteroatom O, S or N. In this procedure, the phenol, thiol, amine or carbinol **314** is reacted with a derivative of a dialkyl hydroxymethyl phosphonate **320**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is OH, SH, NH₂ or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is CH₂OH, a base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **321**, which, employing the sequence of reactions shown in Scheme 45, is transformed into the epoxide

322.

For example, 2-tert.-butoxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid methyl ester, **323** (Fluka) is reacted with a dialkyl trifluoromethanesulfonyloxy phosphonate **138**, prepared as described in Tet. Lett., 1986, 27, 1477, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the ether product **324**. The latter compound is then converted, using the sequence of reactions shown in Scheme 45, into the epoxide **325**.

Using the above procedures, but employing different phenols, thiols, amines and carbinols **314** in place of **323**, and/or different phosphonates **320**, the corresponding products **322** are obtained.

Scheme 47 illustrates the preparation of a phosphonate moiety is attached to the phenylalanine scaffold by means of a heteroatom and a multi-carbon chain.

In this procedure, a substituted phenylalanine derivative 314 is reacted with a dialkyl bromoalkyl phosphonate 146 to afford the product 326. The conditions employed for this reaction are the same as those described above for the preparation of 148, (Scheme 25) The product 326 is then transformed, using the sequence of reactions shown in Scheme 45, into the epoxide 327.

For example, the protected aminoacid 328, prepared as described above (Scheme 45) from 3-mercaptophenylalanine, the preparation of which is described in WO 0036136, is reacted with a dialkyl 2-bromoethyl phosphonate 329, prepared as described in Synthesis, 1994, 9, 909, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the thioether product 330. The latter compound is then converted, using the sequence of reactions shown in Scheme 45, into the epoxide 331.

Using the above procedures, but employing different phenols, thiols, and amines 314 in place of 328, and/or different phosphonates 146, the corresponding products 327 are obtained.

Scheme 48 depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom.

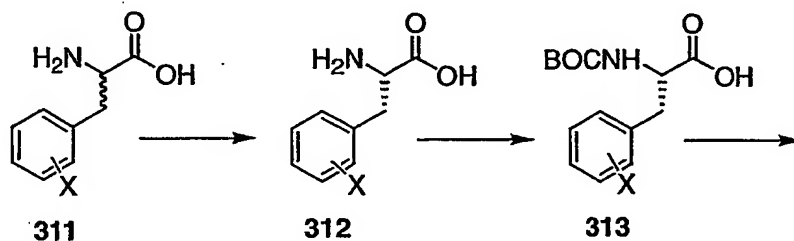
In this procedure, a protected hydroxymethyl-substituted phenylalanine 332 is converted into the halomethyl-substituted compound 333. For example, the carbinol 332 is treated with triphenylphosphine and carbon tetrabromide, as described in J. Amer. Chem. Soc., 108, 1035, 1986 to afford the product 333 in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate 334. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH₂ or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is OH, a strong base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester 335, which, employing the sequence of reactions shown in Scheme 45, is transformed into the epoxide 336.

For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative 337, obtained from the 4-hydroxymethyl phenylalanine, the preparation of which is described in Syn. Comm., 1998, 28, 4279, is converted into the bromo derivative 338, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate 339, the preparation of

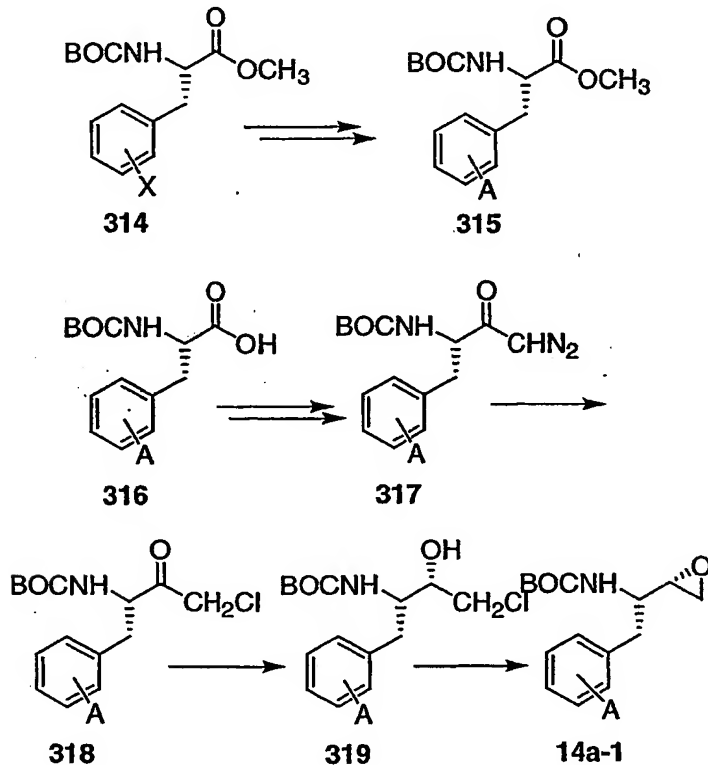
which is described in J. Org. Chem., 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product **340**. The latter compound is then converted, using the sequence of reactions shown in Scheme 45, into the epoxide **341**.

- 5 Using the above procedures, but employing different carbinols **332** in place of **337**, and/or different phosphonates **334**, the corresponding products **336** are obtained.

Scheme 45

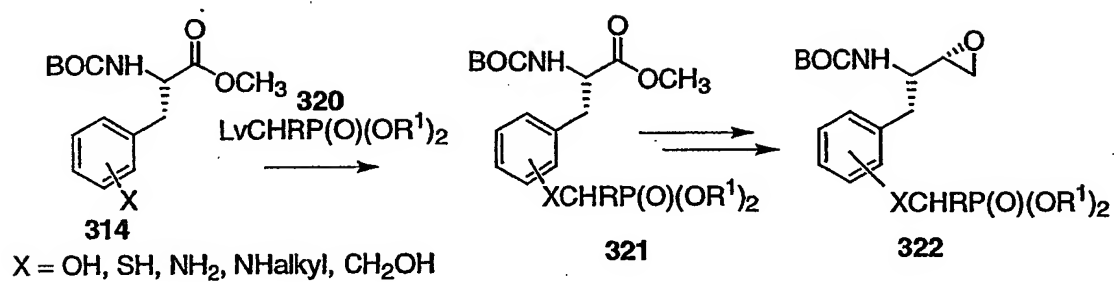


X = OH, SH, NH_2 , NHalkyl, CH_2OH

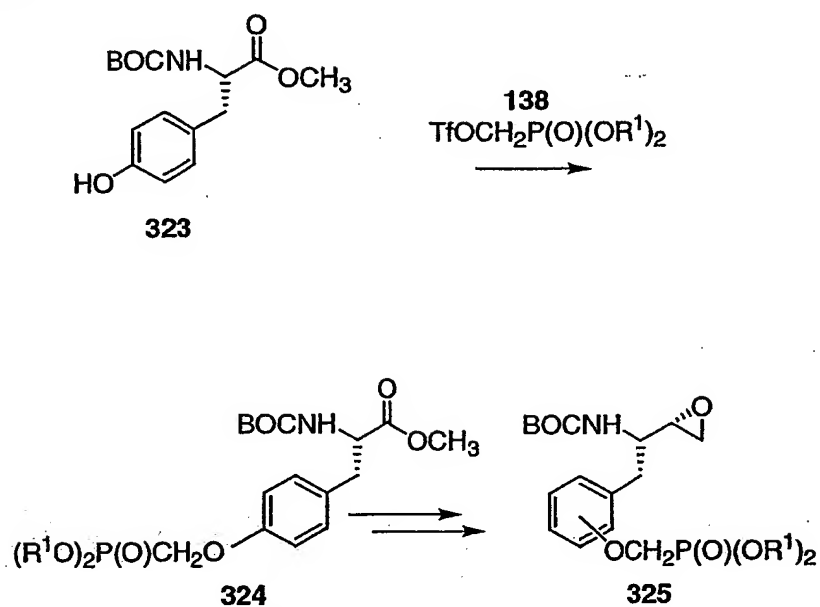


Scheme 46

Method

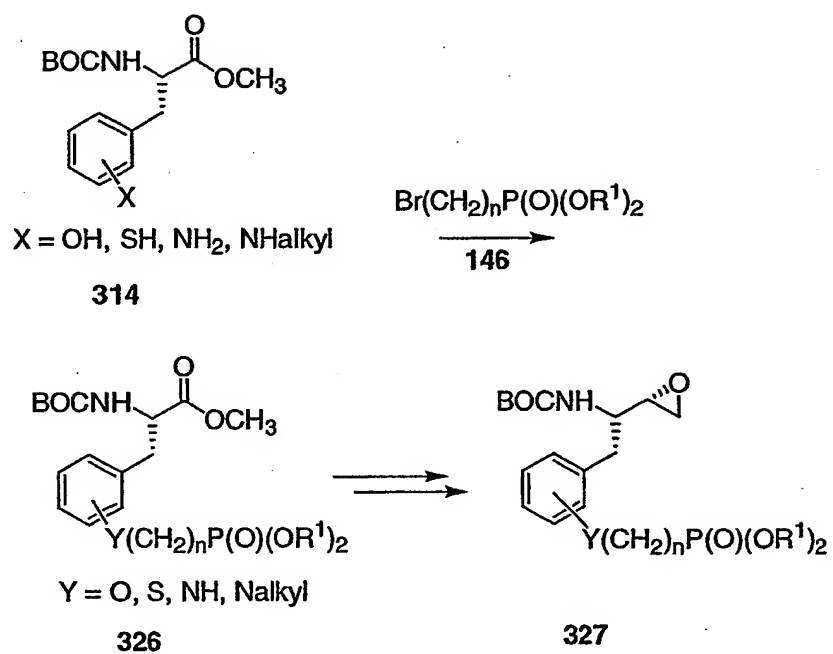


Example

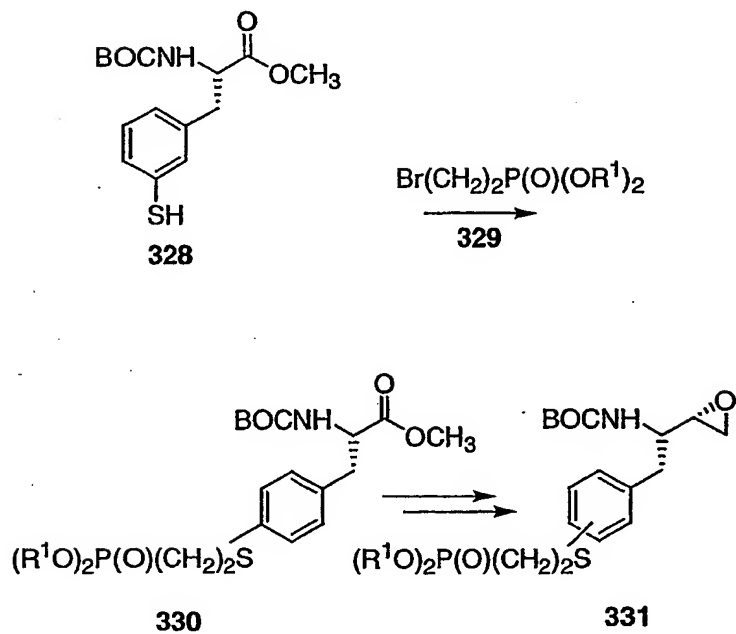


Scheme 47

Method

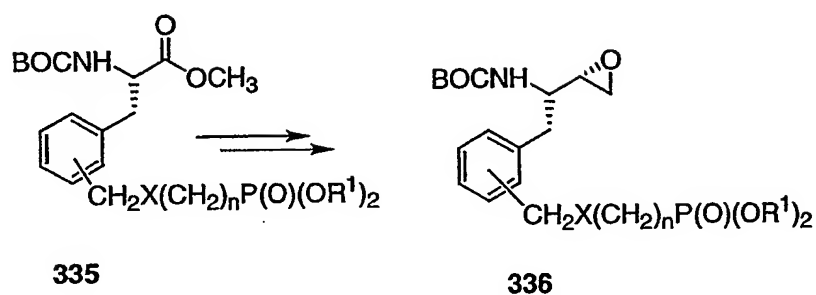
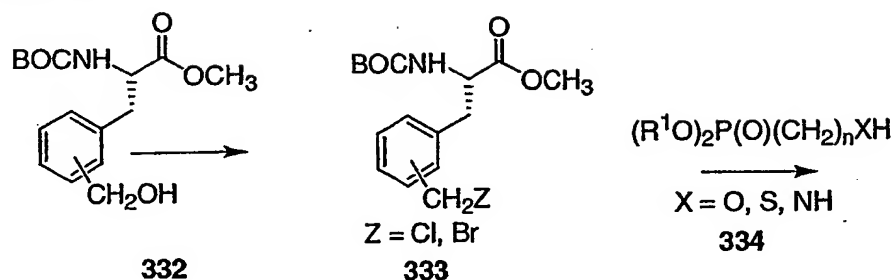


Example

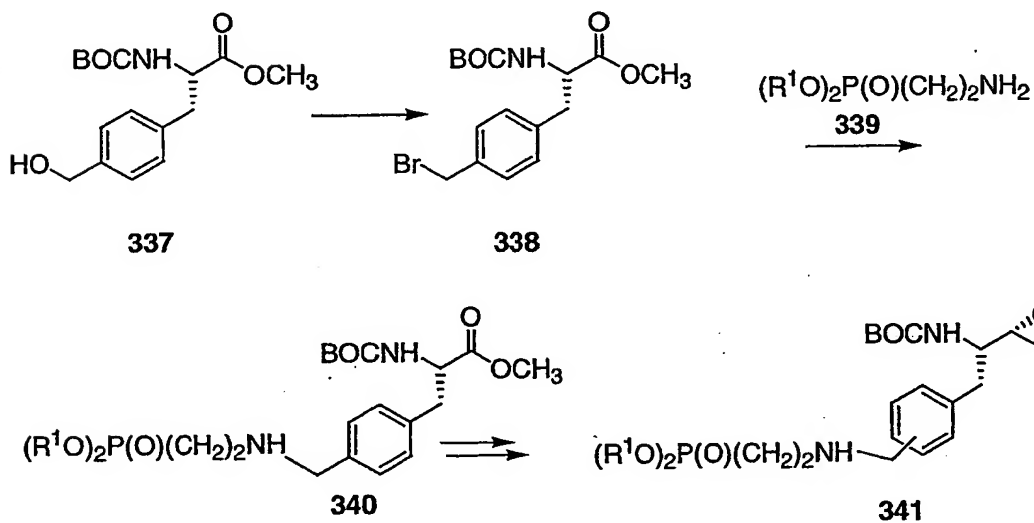


Scheme 48

Method



Example



Interconversions of the phosphonates $\text{R-link-P(O)(OR}^1)_2$, $\text{R-link-P(O)(OR}^1\text{)(OH)}$ and R-link-P(O)(OH)_2 .

Schemes 1-48 describe the preparations of phosphonate esters of the general structure $\text{R-link-P(O)(OR}^1)_2$, in which the groups R^1 , the structures of which are defined in Chart 1, may be the same or different. The R^1 groups attached to phosphonate esters 1-4a, or to precursors thereto,

may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 49. The group R in Scheme 49 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1-4a or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-4a. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 342 into the corresponding phosphonate monoester 343 (Scheme 49, Reaction 1) can be accomplished by a number of methods. For example, the ester 342 in which R¹ is an aralkyl group such as benzyl, can be converted into the monoester compound 343 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester 342 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 343 can be effected by treatment of the ester 342 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

Phosphonate diesters 343 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 343 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, can be converted into the monoester 343 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 342 or a phosphonate monoester 343 into the corresponding phosphonic acid 344 (Scheme 49, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 343

- in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid 344 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester 343 in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid 344 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters 342 in which R^1 is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters 342 in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.
- 10 The conversion of a phosphonate monoester 343 into a phosphonate diester 342 (Scheme 49, Reaction 4) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate 343 is reacted with a hydroxy compound R^1OH , in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a
- 15 carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the
- 20 reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester 342 to the diester 342 can be effected by the use of the Mitsunobu reaction, as described above (Scheme 16). The substrate is reacted with the hydroxy compound R^1OH , in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the
- 25 phosphonate monoester 343 can be transformed into the phosphonate diester 342, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br , in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the
- 30 phosphonate diester in a two step procedure. In the first step, the phosphonate monoester 343 is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in *Organic Phosphorus Compounds*, G. M.

Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $\text{RP(O)(OR}^1\text{)Cl}$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester 342.

- 5 A phosphonic acid R-link-P(O)(OH)_2 can be transformed into a phosphonate monoester $\text{RP(O)(OR}^1\text{)(OH)}$ (Scheme 49, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $\text{R-link-P(O)(OR}^1\text{)}_2$ 342, except that only one molar proportion of the component R^1OH or R^1Br is employed.

- 10 A phosphonic acid R-link-P(O)(OH)_2 344 can be transformed into a phosphonate diester $\text{R-link-P(O)(OR}^1\text{)}_2$ 342 (Scheme 49, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids 344 can be transformed into phosphonic esters 342 in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70° . Alternatively, phosphonic acids 344 can be transformed into phosphonic
15 esters 342 in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester 342.

20 Preparation of carbamates.

- The phosphonate ester compounds 2-4a in which the R^5CO group is derived from the carbonic acid derivatives C38-C49, the structures of which are shown in Chart 4c, are carbamates. The compounds have the general structure $\text{ROCONHR}'$, wherein the
25 substructure ROCO represents the group R^5CO , as defined in Chart 4c, and the substituent R' represents the substructure to which the amine group is attached. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.
30 Scheme 50 illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme 50, in the general reaction generating carbamates, a carbinol 345 is

converted into the activated derivative 346 in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative 346 is then reacted with an amine 347, to afford the carbamate product 348. Examples 1 – 7 in Scheme 50 depict methods by which the general reaction can be effected. Examples 8 - 10 illustrate
5 alternative methods for the preparation of carbamates.

Scheme 50, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol 349. In this procedure, the carbinol 349 is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org.
10 Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate 350. The latter compound is then reacted with the amine component 347, in the presence of an organic or inorganic base, to afford the carbamate 351. For example, the chloroformyl compound 350 is reacted with the amine 347 in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate
15 351. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine..

Scheme 50, Example 2 depicts the reaction of the chloroformate compound 350 with imidazole, 351, to produce the imidazolide 352. The imidazolide product is then reacted with the amine 347 to yield the carbamate 351. The preparation of the imidazolide is performed in
20 an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 50 Example 3, depicts the reaction of the chloroformate 350 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 354. The reaction is conducted
25 in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 363 - 368 shown in Scheme 50, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 363, N-hydroxysuccinimide 364, or pentachlorophenol, 365, the mixed carbonate 354 is obtained by the reaction of the
30 chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 366 or 2-hydroxypyridine 367 can be performed in

an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme 50 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 352 is employed. In this procedure, a carbinol 349 is reacted with an equimolar amount of carbonyl diimidazole 355 to prepare the intermediate 352. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 352 is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 351. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 351.

Scheme 50, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxy carbonyl benzotriazole 357. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benzotriazole carbonyl chloride 356, to afford the alkoxy carbonyl product 357. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine $R'NH_2$ to afford the carbamate 351. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80° as described in Syn., 1977, 704.

Scheme 50, Example 6 illustrates the preparation of carbamates in which a carbonate $(R''O)_2CO$, 358, is reacted with a carbinol 349 to afford the intermediate alkyloxycarbonyl intermediate 359. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate 351. The procedure in which the reagent 359 is derived from hydroxybenzotriazole 363 is described in Synthesis, 1993, 908; the procedure in which the reagent 359 is derived from N-hydroxysuccinimide 364 is described in Tet. Lett., 1992, 2781; the procedure in which the reagent 359 is derived from 2-hydroxypyridine 367 is described in Tet. Lett., 1991, 4251; the procedure in which the reagent 359 is derived from 4-nitrophenol 368 is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate 358 is conducted in an inert organic solvent at ambient temperature.

Scheme 50, Example 7 illustrates the preparation of carbamates from alkoxy carbonyl azides 360. In this procedure, an alkyl chloroformate 350 is reacted with an azide, for example sodium azide, to afford the alkoxy carbonyl azide 360. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 351. The reaction is

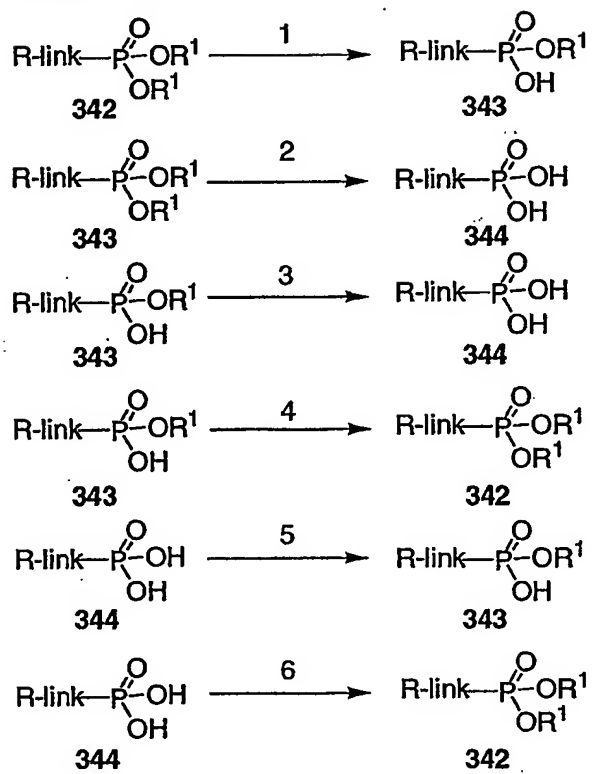
conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme 50, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate 351.

Scheme 50, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate 362. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate 351.

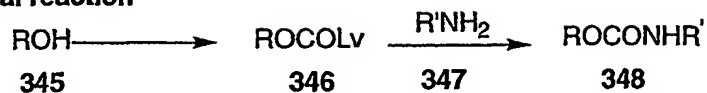
Scheme 50, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate 351.

Scheme 49

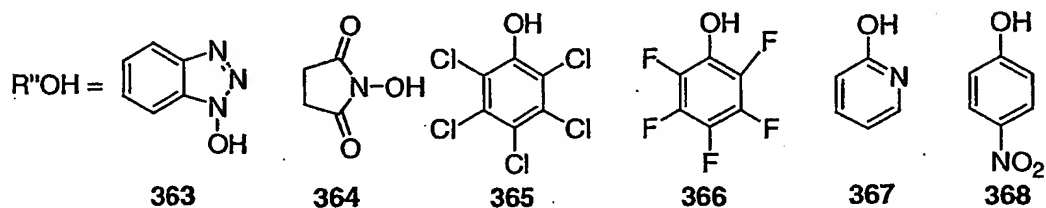
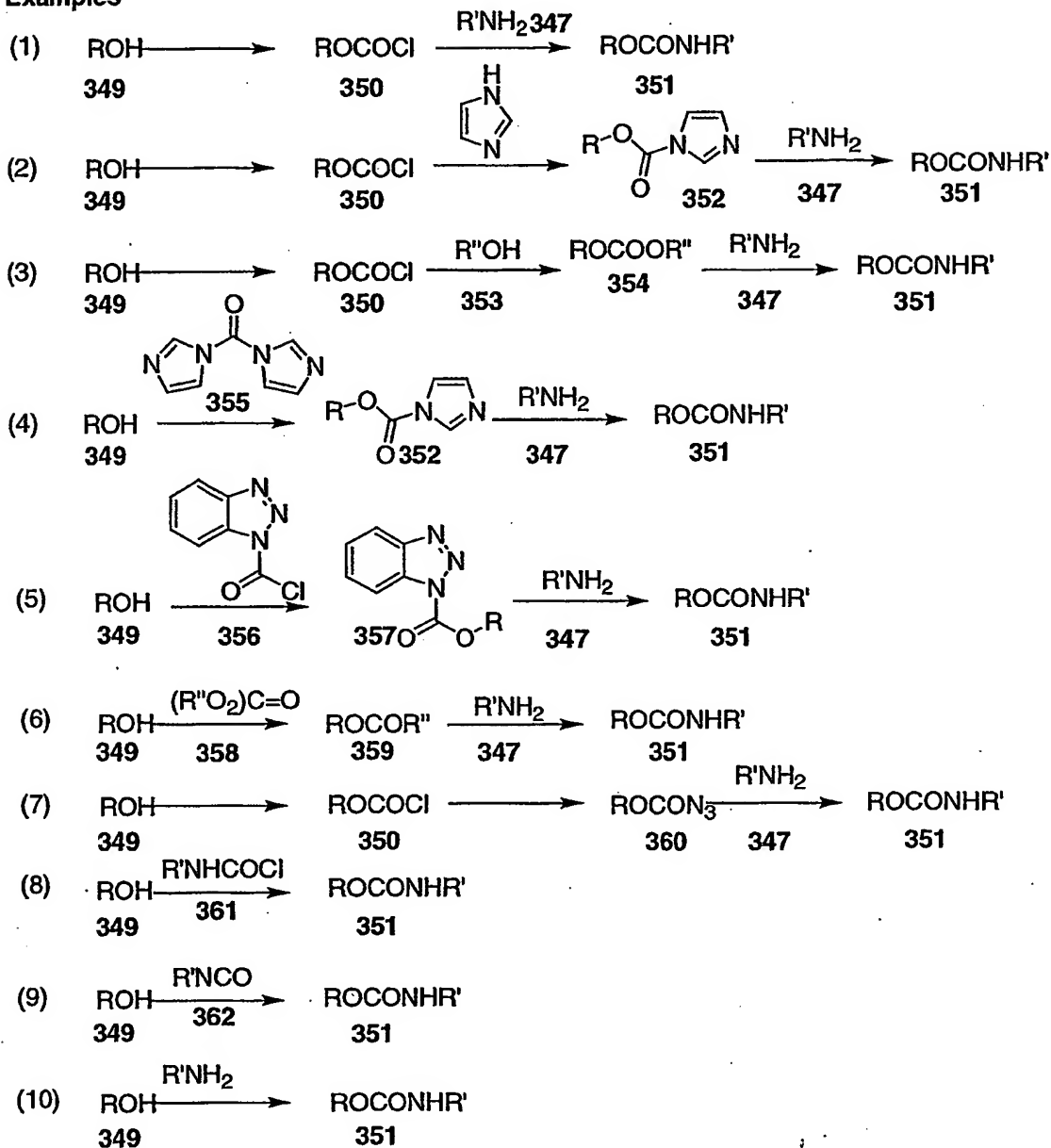


Scheme 50

General reaction



Examples



General applicability of methods for introduction of phosphonate substituents.

The above-described methods for the preparation of phosphonate-substituted thiols, Schemes
5 20 to 30, can, with appropriate modifications according to the knowledge of one skilled in the art, be applied to the preparation of phosphonate-substituted benzoic acids, tert-butylamines, decahydroisoquinolines and phenylalanines.

Similarly, preparative methods described above for phosphonate-substituted benzoic acids, tert-butylamines, decahydroisoquinolines and phenylalanines, Schemes 31 to 48, can, with
10 appropriate modifications according to the knowledge of one skilled in the art, be applied to the preparation of phosphonate-substituted thiophenols.

Preparation of compounds 1-4a with phosphonate moieties attached to any substructural component.

15 The chemical transformations described in Schemes 1-50 illustrate the preparation of compounds 1-4 in which the phosphonate ester moiety is attached to the hydroxymethyl benzoic acid group (Schemes 1-3), the phenylthio moiety (Schemes 4-6), the amine moiety (Schemes 7-9), the decahydroisoquinoline moiety (Schemes 10-12) and the phenyl moiety
20 (Schemes 10-14b).

Charts 2 - 4 illustrate various chemical substructures that may be substituted for the phosphonate-containing moieties. For example, in Chart 2, substructures 6, 7 and 8-20e may be substituted for the decahydroisoquinoline moiety, and in Chart 3, substructures 21-26 may be substituted for the group CH_2XR^4 in compounds 1-4. Charts 4a-c illustrate the structures
25 of the compounds R^5COOH which may be incorporated into the phosphonate esters 2-4.

By utilization of the methods described herein for the preparation of, and incorporation of phosphonate-containing moieties, and by the application of the knowledge of one skilled in the art, the phosphonate ester moieties described herein may be incorporated into the amines 6, 7, and 8-20, into the R^4 groups 21-26, and into the carboxylic acids, or functional equivalents
30 thereof, with the structures C1-C49. Subsequently, the thus-obtained phosphonate-ester containing moieties may, utilizing the procedures described above in Schemes 1-14b, be incorporated into the compounds represented by the formula 4a (Chart 1) in which one of the

groups R^2NHCR^3 , R^4 , R^5 or Bu^t contains a phosphonate group of the general formula link- $P(O)(OR^1)_2$.

Lopinavir-like phosphonate protease inhibitors (LLPPI)

5

Preparation of the intermediate phosphonate esters.

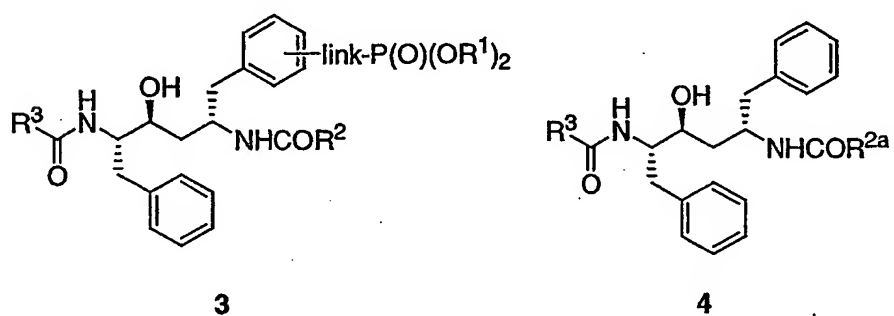
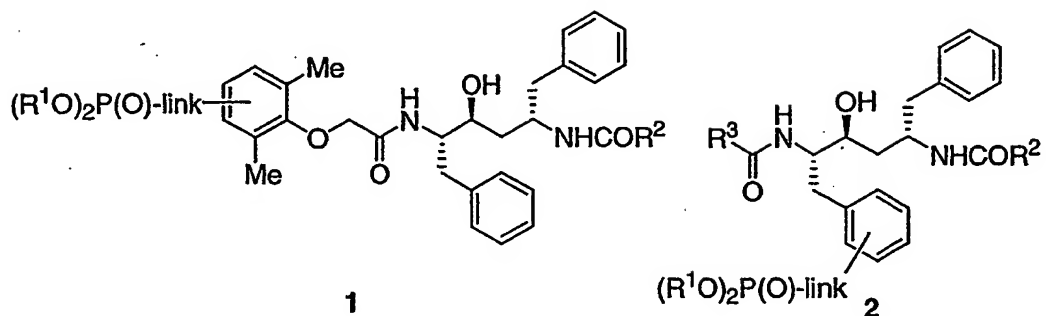
The structures of the intermediate phosphonate esters 1 to 5 and the structures for the component groups R^1 of this invention are shown in Chart 1.

10 The structures of the R^2COOH and R^3OOH components C1- C49 are shown in Charts 2a, 2b and 2c. Specific stereoisomers of some of the structures are shown in Charts 1, and 2; however, all stereoisomers are utilized in the syntheses of the compounds 1 to 5. Subsequent chemical modifications to the compounds 1 to 5, as described herein, permit the synthesis of the final compounds of this invention.

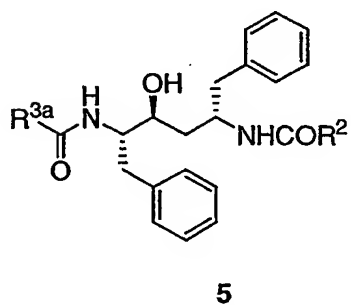
15 The intermediate compounds 1 to 5 incorporate a phosphonate moiety connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts 4 and 5 illustrate examples of the linking groups present in the structures 1 – 5, and in which "etc" refers to the scaffold, e.g., lopinavir.

20 Schemes 1 - 33 illustrate the syntheses of the intermediate phosphonate compounds of this invention, 1- 3, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters 4 and 5, in which the phosphonate moiety is incorporated into different members of the groups R^2COOH and R^3COOH , is also described below.

Chart 1 Intermediate phosphonate esters

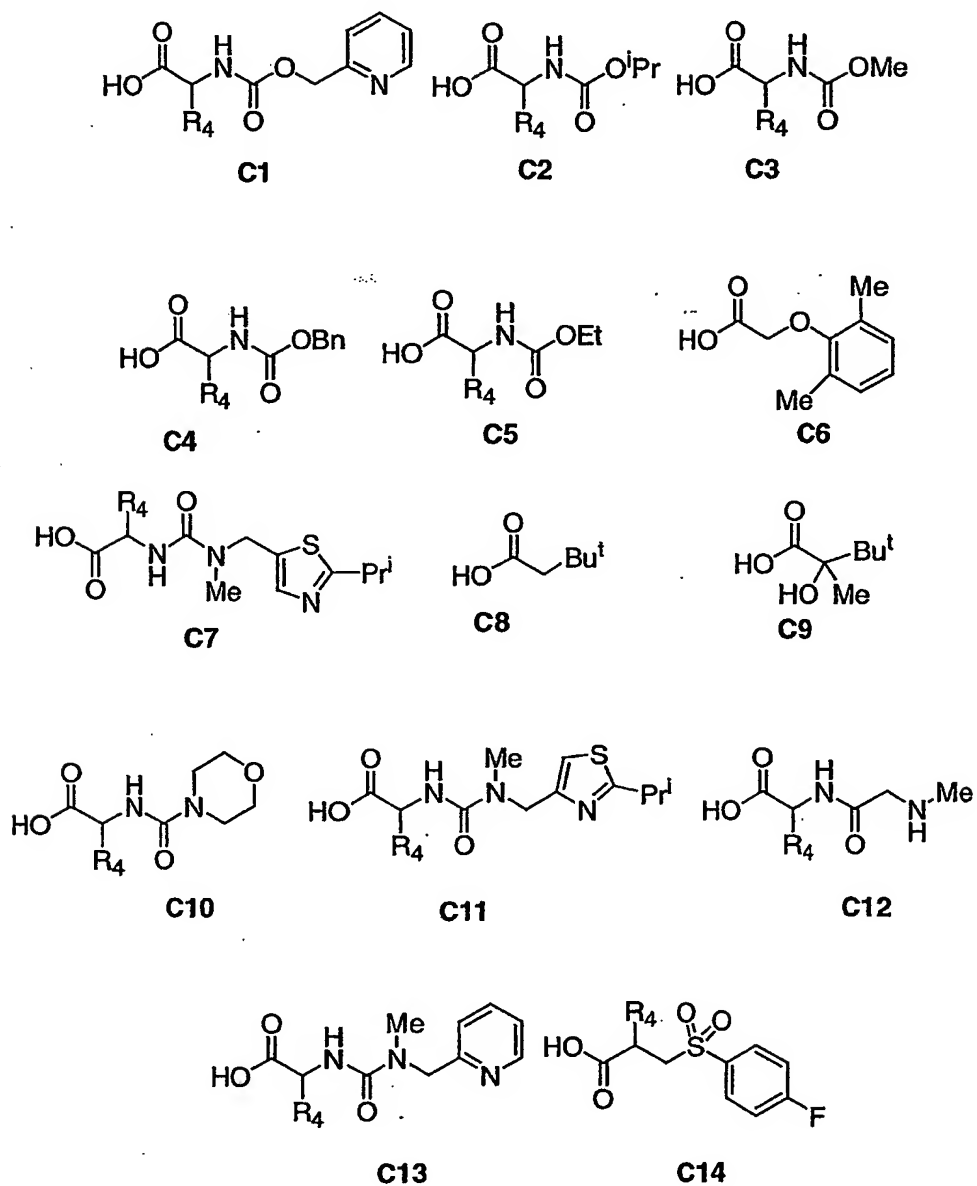


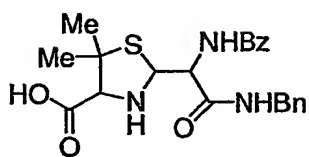
R^{2a} = phosphonate-containing R^2



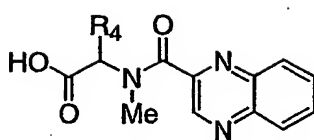
R^{3a} = phosphonate-containing R^3

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

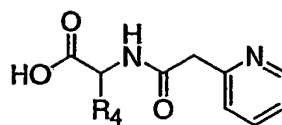
Chart 2a Structures of the R²COOH and R³COOH components



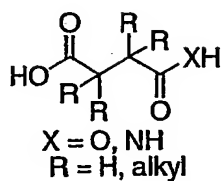
C15



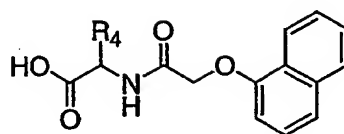
C16



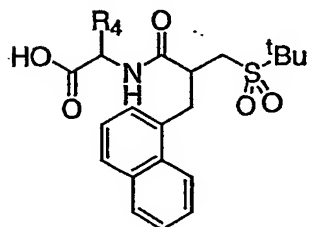
C17



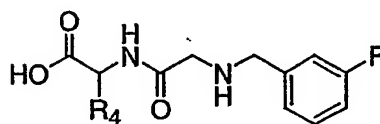
C18



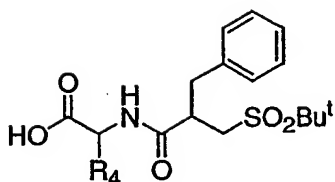
C19



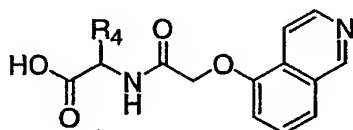
C20



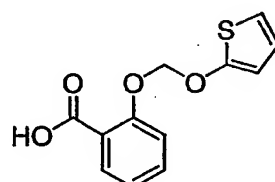
C21



C22

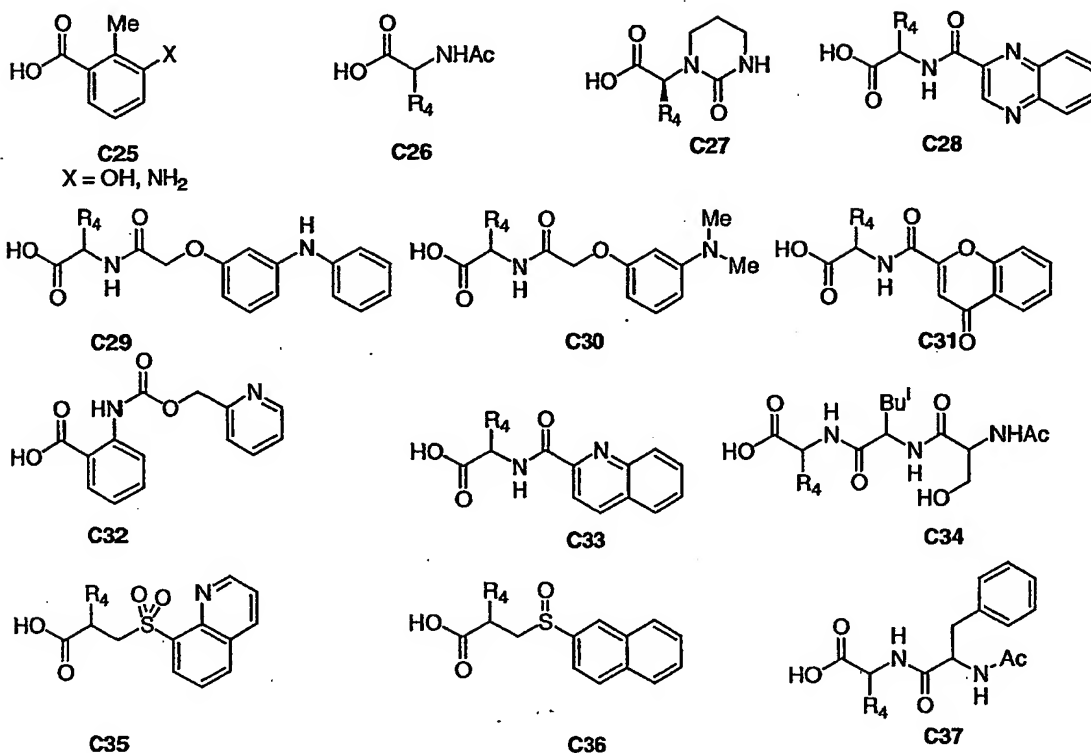


C23

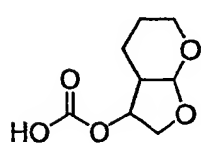


C24

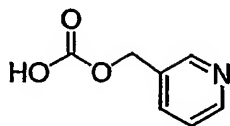
R^4 = alkyl, $\text{CH}_2\text{SO}_2\text{CH}_3$, $\text{C}(\text{CH}_3)_2\text{SO}_2\text{CH}_3$, CH_2CONH_2 , CH_2SCH_3 , imidaz-4-ylmethyl, CH_2NHAc , $\text{CH}_2\text{NHCOCF}_3$

Chart 2b Structures of the R²COOH and R³COOH components

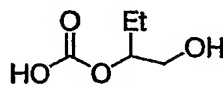
R⁴ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

Chart 2c Structures of the R²COOH and R³COOH components

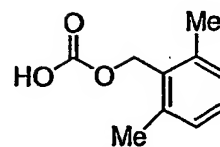
C38



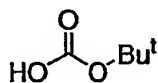
C39



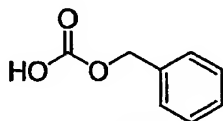
C40



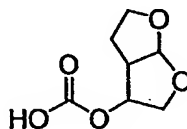
C41



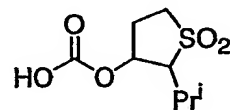
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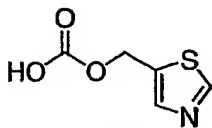
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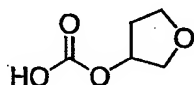
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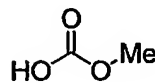
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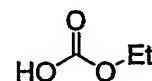
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C47



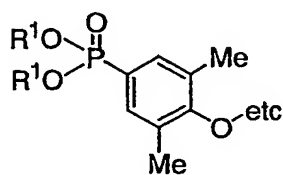
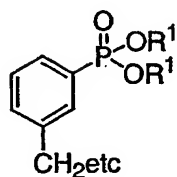
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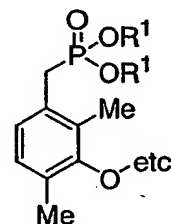
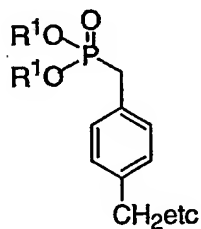
C49

Chart 4 Examples of the linking group between the scaffold and the phosphonate moiety.**link****examples**

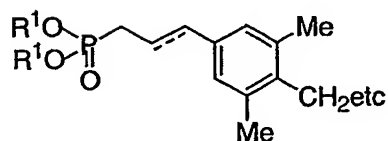
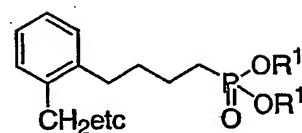
direct bond



single carbon



multiple carbon



hetero atoms

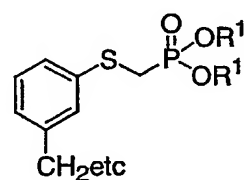
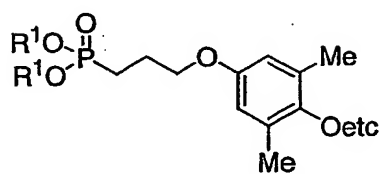
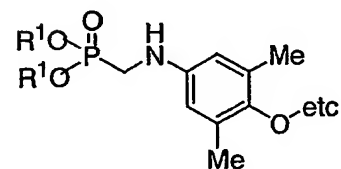
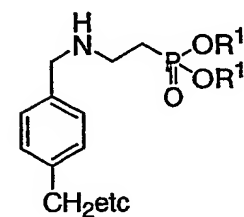
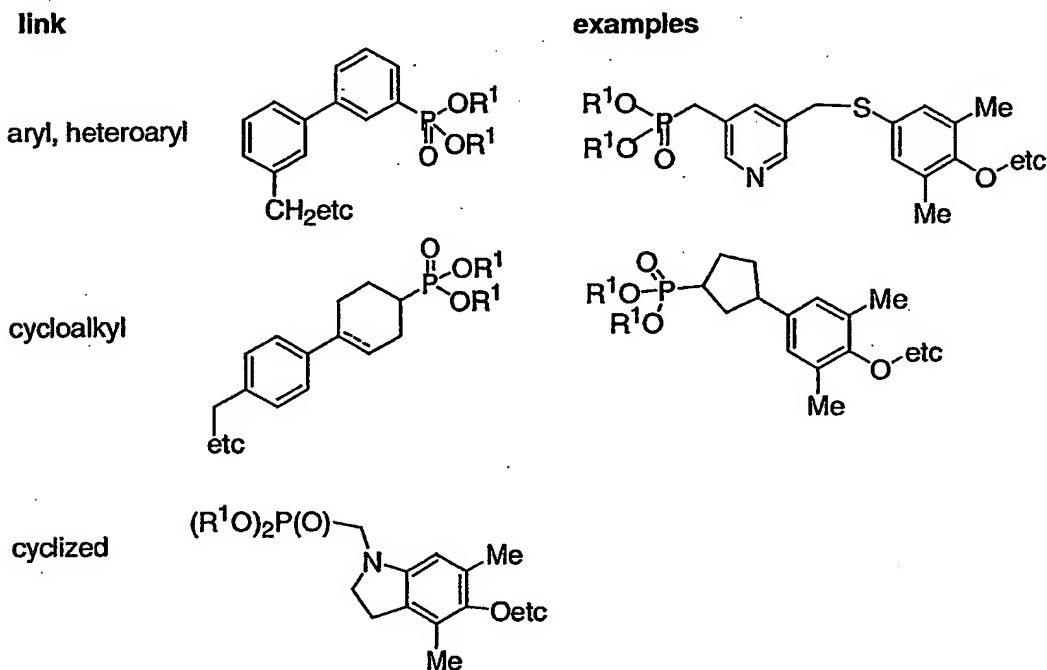


Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.**Protection of reactive substituents.**

5

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990.

Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

10

Preparation of the phosphonate intermediates 1.

15

Two methods for the preparation of the phosphonate intermediate compounds 1 are shown in Schemes 1 and 2. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme 1, 5-amino-2-dibenzylamino-1,6-diphenyl-hexan-3-ol, **1.1**, the preparation of which is described in Org. Process Res. Dev., 1994, 3, 94, is reacted with a carboxylic acid R^2COOH , or an activated derivative **1.2** thereof, to produce the amide **1.3**. The preparation of amides from carboxylic acids and derivatives is described, for example, in
5 Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of hydroxybenzotriazole, in a non-protic solvent such as, for example, pyridine, DMF or
10 dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

- 15 The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid is converted into the acid chloride **1.2**, $X = Cl$, and the latter compound is reacted with an equimolar amount of the amine **1.1**, in an aprotic solvent such as,
20 for example, tetrahydrofuran, at ambient temperature. The reaction is conducted in the presence of an organic base such as triethylamine, so as to afford the amide product **1.3**.

The N, N-dibenzylamino amide product **1.3** is then transformed into the free amine compound **1.4** by means of a debenzylation procedure. The deprotection of N-benzyl amines is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and
25 P.G.M Wuts, Wiley, Second Edition 1990, p. 365. The transformation can be effected under reductive conditions, for example by the use of hydrogen or a hydrogen transfer agent, in the presence of a palladium catalyst, or by treatment of the N-benzyl amine with sodium in liquid ammonia, or under oxidative conditions, for example by treatment with 3-chloroperoxybenzoic acid and ferrous chloride.

- 30 Preferably, the N, N-dibenzyl compound **1.3** is converted into the amine **1.4** by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic

ammonium formate and 5% palladium on carbon catalyst, at ca. 75° for ca. 6 hours, for example as described in U.S. Patent 5,914,332.

The thus-obtained amine 1.4 is then transformed into the amide 1.5 by reaction with the carboxylic acid 1.6, or an activated derivative thereof, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH], [NH], [CHO], Br, as described below. Preparations of the carboxylic acids 1.6 are described below, Schemes 9-14. The amide-forming reaction is conducted under similar conditions to those described above for the preparation of the amide 1.3.

Preferably, the carboxylic acid 1.6 is converted into the acid chloride, and the acid chloride is reacted with the amine 1.4 in a solvent mixture composed of an organic solvent such as ethyl acetate, and water, in the presence of a base such as sodium bicarbonate, for example as described in Org. Process Res. Dev., 2000, 4, 264, to afford the amide product 1.5.

Alternatively, the amide 1.5 can be obtained by the procedure shown in Scheme 2. In this method, 2-tert-butoxycarbonylamino-5-methyl-1,6-diphenyl-hexan-3-ol, 2.1, the preparation of which is described in U.S. Patent 5,4912,53, is reacted with the carboxylic acid 1.6, or an activated derivative thereof, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto. The reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.5.

Preferably, equimolar amounts of the amine 2.1 and the carboxylic acid 1.6 are reacted in dimethylformamide in the presence of a carbodiimide, such as, for example, 1-dimethylaminopropyl-3-ethylcarbodiimide, as described, for example, in U.S. Patent 5,914,332, to yield the amide 2.2.

The tert-butoxycarbonyl (BOC) protecting group is then removed from the product 2.2 to afford the free amine 2.3. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preferably, the BOC group is removed by treatment of the substrate 2.2 with trifluoroacetic acid in dichloromethane at ambient temperature, for example as described in U.S. Patent 5,9142,32, to afford the free amine product 2.3.

The amine product 2.3 is then reacted with the acid R^2COOH 2.4, or an activated derivative thereof, to produce the amide 2.5. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.5.

Preferably, equimolar amounts of the amine 2.3 and the carboxylic acid 2.4 are reacted in
5 dimethylformamide in the presence of a carbodiimide, such as, for example, 1-dimethylaminopropyl-3-ethylcarbodiimide, as described, for example, in U.S. Patent 5,914,332, to yield the amide 1.5.

The reactions illustrated in Schemes 1 and 2 illustrate the preparation of the compounds 1.5 in
10 which A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH, as described below. Scheme 3 depicts the conversion of the compounds 1.5 in which A is OH, SH, NH, as described below, into the compounds 1 in which A is the group $link-P(O)(OR^1)_2$. In this procedure, the compounds 1.5 are converted, using the procedures described below, Schemes 9-33, into the compounds 1.

15

Preparation of the phosphonate intermediates 2.

Two methods for the preparation of the phosphonate intermediate compounds 2 are shown in Schemes 4 and 5. The selection of the route to be employed for a given compound is made
20 after consideration of the substituents which are present, and their stability under the reaction conditions required.

As depicted in Scheme 4, the tribenzylated phenylalanine derivative 4.1, in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, as described below, is reacted with the anion 4.2 derived from acetonitrile, to afford the ketonitrile 4.3. Preparations
25 of the tribenzylated phenylalanine derivatives 4.1 are described below, Schemes 15-17.

The anion of acetonitrile is prepared by the treatment of acetonitrile with a strong base, such as, for example, lithium hexamethyldisilylazide or sodium hydride, in an inert organic solvent such as tetrahydrofuran or dimethoxyethane, as described, for example, in U.S. Patent 5,491,253. The solution of the acetonitrile anion 4.2, in an aprotic solvent such as
30 tetrahydrofuran, dimethoxyethane and the like, is then added to a solution of the ester 4.1 at low temperature, to afford the coupled product 4.3.

Preferably, a solution of ca. two molar equivalent of acetonitrile, prepared by the addition of ca. two molar equivalent of sodium amide to a solution of acetonitrile in tetrahydrofuran at -40° , is added to a solution of one molar equivalent of the ester 4.1 in tetrahydrofuran at -40° , as described in J. Org. Chem., 1994, 59, 4040, to produce the ketonitrile 4.3.

5 The above-described ketonitrile compound 4.3 is then reacted with an organometallic benzyl reagent, such as a benzyl Grignard reagent or benzyllithium, to afford the ketoenamine 4.5. The reaction is conducted in an inert aprotic organic solvent such as diethyl ether, tetrahydrofuran or the like, at from -80° to ambient temperature, to yield the benzylated product 4.5.

10 Preferably, the ketonitrile 4.3 is reacted with three molar equivalents of benzylmagnesium chloride in tetrahydrofuran at ambient temperature, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine 4.5.

The ketoenamine 4.5 is then reduced, in two stages, via the ketoamine 4.6, to produce the
15 amino alcohol 4.7. The transformation of the compound 4.5 to the aminoalcohol 4.7 can be effected in one step, or in two steps, with or without isolation of the intermediate ketoamine 4.6, as described in U.S. Patent 5,491,253.

For example, the ketoenamine 4.5 is reduced with a boron-containing reducing agent such as sodium borohydride, sodium cyanoborohydride and the like, in the presence of an acid such as
20 methanesulfonic acid, as described in J. Org. Chem., 1994, 59, 4040, to afford the ketoamine 4.6. The reaction is performed in an ethereal solvent such as, for example, tetrahydrofuran or methyl tert-butyl ether. The product 4.6 is then reduced with sodium borohydride-trifluoroacetic acid, as described in U.S. Patent 5,491,253, to afford the aminoalcohol 4.7.

Alternatively, the ketoenamine 4.5 can be reduced to the aminoalcohol 4.7 without isolation of
25 the intermediate ketoamine 4.6. In this procedure, as described in U.S. Patent 5,491,253, the ketoenamine 4.5 is reacted with sodium borohydride-methanesulfonic acid, in an ethereal solvent such as dimethoxyethane and the like. The reaction mixture is then treated with a quenching agent such as triethanolamine, and the procedure is continued by the addition of sodium borohydride and a solvent such as dimethylformamide or dimethylacetamide or the
30 like, to afford the aminoalcohol 4.7.

The aminoalcohol 4.7 is converted into the amide 4.8 by reaction with the acid R^2COOH 2.4 or an activated derivative thereof, to produce the amide 4.8. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.5.

The dibenzylated amide product 4.8 is then deprotected to afford the free amine 4.9. The

5 conditions for the debenzylation reaction are the same as those described above for the deprotection of the dibenzyl amine 1.3 to yield the amine 1.4, (Scheme 1).

The amine 4.9 is then reacted with the carboxylic acid R^3COOH (4.10) as defined in Charts 2a-2c, or an activated derivative thereof, to produce the amide 4.11. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and

10 1.5.

Alternatively, the amide 4.11 can be prepared by means of the sequence of reactions illustrated in Scheme 5.

In this sequence, the tribenzylated amino acid derivative 4.1 is converted, by means of the reaction sequence shown in Scheme 4, into the dibenzylated amine 4.7. This compound is then
15 converted into a protected derivative, for example the tert-butoxycarbonyl (BOC) derivative 5.1. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 327. For example, the amine can be reacted with di-tert-butoxycarbonylanhydride (BOC anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-
20 ON), and the like.

Preferably, the amine 4.7 is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in US Patent 59143332, to yield the BOC-protected product 5.1.

The N-benzyl protecting groups are then removed from the amide product 5.1 to afford the
25 free amine 5.2. The conditions for this transformation are similar to those described above for the preparation of the amine 1.4, (Scheme 1).

Preferably, the N, N-dibenzyl compound 5.1 is converted into the amine 5.2 by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic ammonium formate and 5% palladium on carbon catalyst, at ca. 75° for ca. 6 hours, for
30 example as described in US Patent 5914332

The amine compound 5.2 is then reacted with the carboxylic acid R^3COOH , or an activated derivative thereof, to produce the amide 5.3. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.5, (Scheme 1).

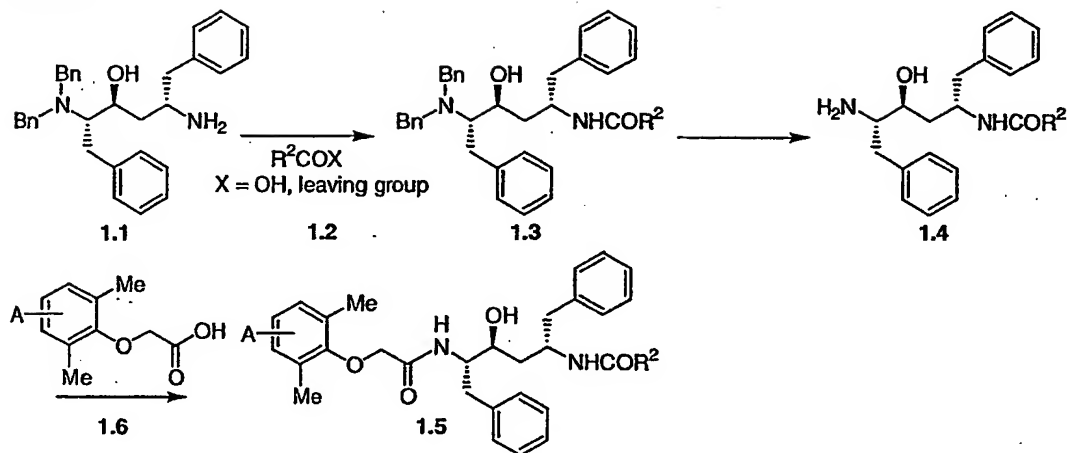
The BOC-protected amide 5.3 is then converted into the amine 5.4 by removal of the BOC protecting group. The conditions for this transformation are similar to those described above for the preparation of the amine 2.3 (Scheme 2). The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preferably, the BOC group is removed by treatment of the substrate 5.3 with trifluoroacetic acid in dichloromethane at ambient temperature, for example as described in US Patent 5914232, to afford the free amine product 5.4.

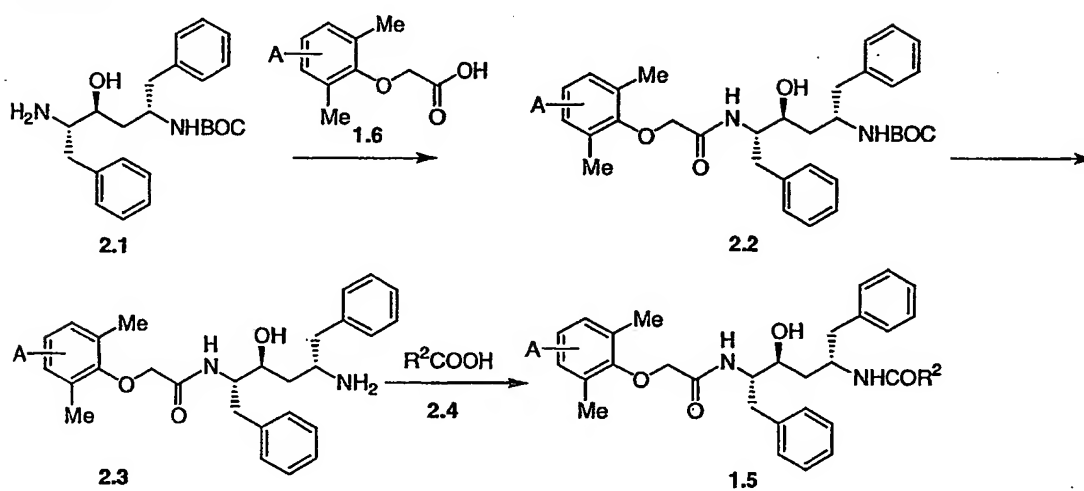
The free amine thus obtained is then reacted with the carboxylic acid R^2COOH 2.4, or an activated derivative thereof, to produce the amide 4.11. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.5.

The reactions shown in Schemes 4 and 5 illustrate the preparation of the compounds 4.11 in which A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH, as described below. Scheme 6 depicts the conversion of the compounds 4.11 in which A is OH, SH, NH, as described below, into the compounds 2. In this procedure, the compounds 4.11 are converted, using the procedures described below, Schemes 9-33, into the compounds 2.

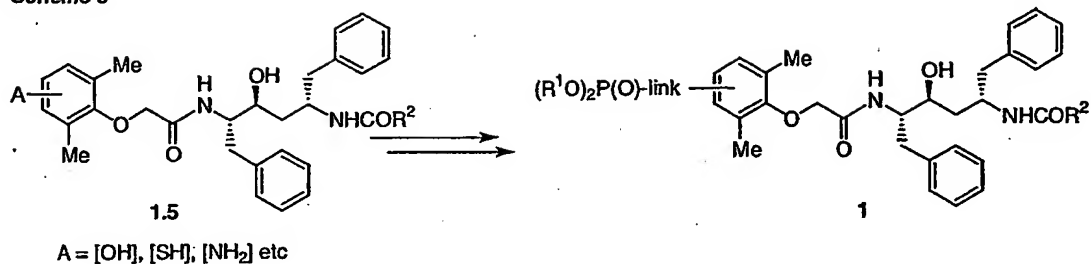
Scheme 1



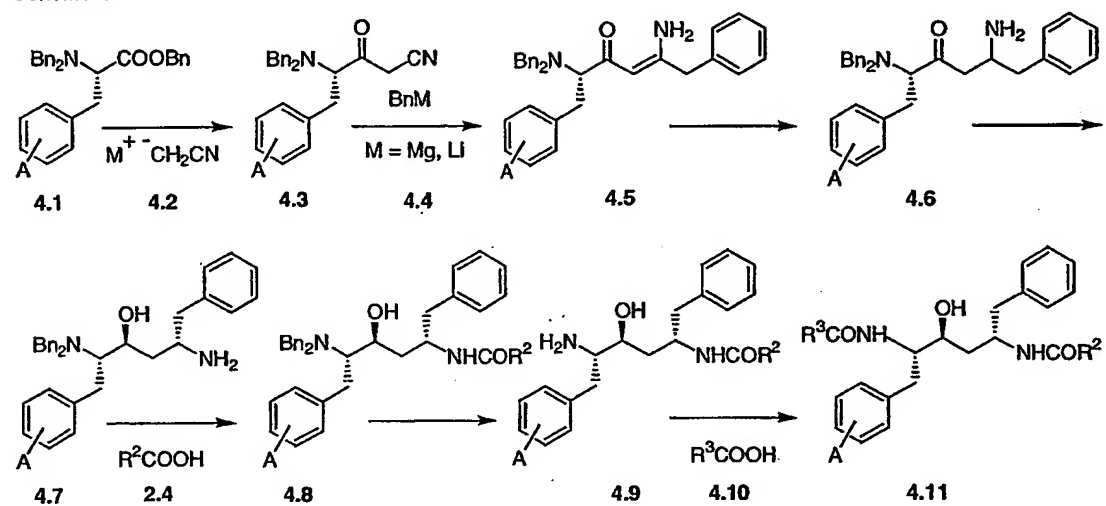
Scheme 2



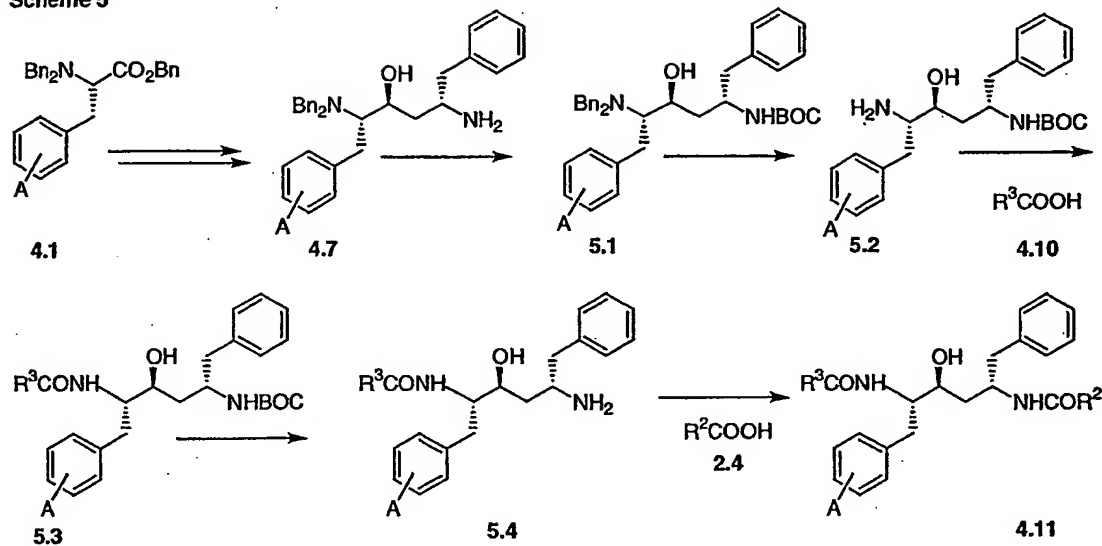
Scheme 3



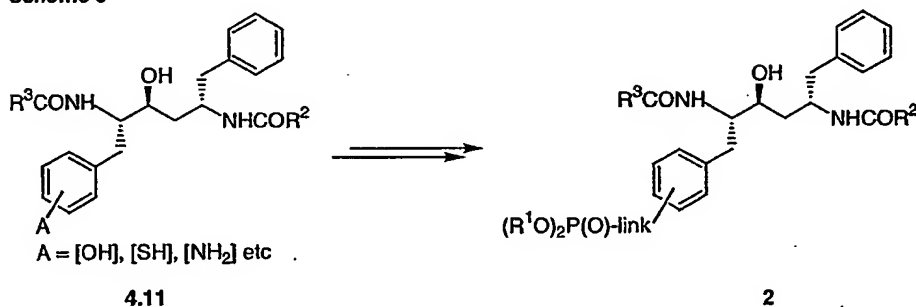
Scheme 4



Scheme 5



Scheme 6



Preparation of the phosphonate intermediates 3.

- 5 The phosphonate ester intermediate compounds 3 can be prepared by two alternative methods, illustrated in Schemes 7 and 8. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.
- As shown in Scheme 7, 4-dibenzylamino-3-oxo-5-phenyl-pentanenitrile 7.1, the preparation of which is described in J. Org. Chem., 1994, 59, 4040, is reacted with a substituted
- 10 benzylmagnesium halide reagent 7.2, in which the group B is a substituent, protected if appropriate, which can be converted, after the sequence of reactions shown in Scheme 7, into the substituent link-P(O)(OR¹)₂. Examples of the substituent B are Br, [OH], [SH], [NH₂]

[CHO] and the like; procedures for the transformation of these groups into the phosphonate moiety are shown below in Schemes 9-33.

The conditions for the reaction between the benzylmagnesium halide 7.2 and the ketonitrile 7.1 are similar to those described above for the preparation of the ketoenamine 4.5 (Scheme 4). Preferably, the ketonitrile 7.1 is reacted with three molar equivalents of the substituted benzylmagnesium chloride 7.2 in tetrahydrofuran at ca. 0°, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine 7.3.

The thus-obtained ketoenamine 7.3 is then transformed, via the intermediate compounds 7.4, 7.5, 7.6 and 7.7 into the diacylated carbinol 7.8. The conditions for each step in the conversion of the ketoenamine 7.3 to the diacylated carbinol 7.8 are the same as those described above (Scheme 4) for the transformation of the ketoenamine 4.5 into the diacylated carbinol 4.11. The diacylated carbinol 7.8 is then converted into the phosphonate ester 3, using procedures illustrated below in Schemes 9-33.

Alternatively, the phosphonate esters 3 can be obtained by means of the reactions illustrated in Scheme 8. In this procedure, the amine 7.4, the preparation of which is described above, (Scheme 7) is converted into the BOC derivative 8.1. The conditions for the introduction of the BOC group are similar to those described above for the conversion of the amine 4.7 into the BOC-protected product 5.1, (Scheme 5).

Preferably, the amine 7.4 is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in US Patent 5914332, to yield the BOC-protected product 8.1.

The BOC-protected amine 8.1 is then converted, via the intermediates 8.2, 8.3 and 8.4 into the diacylated carbinol 7.8. The reaction conditions for this sequence of reactions are similar to those described above for the transformation of the BOC-protected amine 5.1 into the diacylated carbinol 4.11 (Scheme 5).

The diacylated carbinol 7.8 is then converted into the phosphonate ester 3, using procedures illustrated below in Schemes 18-20.

Preparation of dimethylphenoxyacetic acids incorporating phosphonate moieties.

Scheme 9 illustrates two alternative methods by means of which 2,6-dimethylphenoxyacetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the 2,6-dimethylphenol moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed 2,6-

5 dimethylphenoxyacetic acid intermediate. In the first sequence, a substituted 2,6-dimethylphenol 9.1, in which the substituent B is a precursor to the group $\text{link-P(O)(OR}^1\text{)}_2$, and in which the phenolic hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound 9.2. Methods for the conversion of the substituent B into the group $\text{link-P(O)(OR}^1\text{)}_2$ are described below in

10 Schemes 9 - 33.

The protected phenolic hydroxyl group present in the phosphonate-containing product 9.2 is then deprotected, using methods described below, to afford the phenol 9.3.

The phenolic product 9.3 is then transformed into the corresponding phenoxyacetic acid 9.4, in a two step procedure. In the first step, the phenol 9.3 is reacted with an ester of

15 bromoacetic acid 9.5, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of phenols to afford phenolic ethers is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the phenol and the

20 alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol 9.3 and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described

25 in US Patent 5914332, to afford the ester 9.6.

The thus-obtained ester 9.6 is then hydrolyzed to afford the carboxylic acid 9.4. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group,

30 methods for hydrolysis are described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

Preferably, the ester product 9.6 which R is ethyl is hydrolyzed to the carboxylic acid 9.4 by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in US Patent 5914332.

Alternatively, an appropriately substituted 2,6-dimethylphenol 9.7, in which the substituent B is a precursor to the group link-P(O)(OR¹)₂, is transformed into the corresponding phenoxyacetic ester 9.8. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol 9.3 into the ester 9.6.

The phenolic ester 9.8 is then converted, by transformation of the group B into the group link-P(O)(OR¹)₂ followed by ester hydrolysis, into the carboxylic acid 9.4. The group B which is present in the ester 9.4 may be transformed into the group link-P(O)(OR¹)₂ either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes 9-14 illustrate the preparation of 2,6-dimethylphenoxyacetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of phenoxyacetic esters acids 9.8, with, if appropriate, modifications made according to the knowledge of one skilled in the art..

Scheme 10 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester which is attached to the phenolic group by means of a carbon chain incorporating a nitrogen atom. The compounds 10.4 are obtained by means of a reductive alkylation reaction between a 2,6-dimethylphenol aldehyde 10.1 and an aminoalkyl phosphonate ester 10.2. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component 10.2 and the aldehyde component 10.1 are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product 10.3. The amination product 10.3 is then converted into the phenoxyacetic acid compound 10.4, using the alkylation and ester hydrolysis procedures described above, (Scheme 9) For example, equimolar amounts of 4-hydroxy-3,5-dimethylbenzaldehyde 10.5 (Aldrich) and a dialkyl aminoethyl phosphonate 10.6, the preparation of which is described in J. Org. Chem., 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic

acid, as described, for example, in J. Amer. Chem. Soc., 91, 3996, 1969, to afford the amine product 10.3. The product is then converted into the acetic acid 10.8, as described above. Using the above procedures, but employing, in place of the aldehyde 10.5, different aldehydes 10.1, and/or different aminoalkyl phosphonates 10.2, the corresponding products 10.4 are
5 obtained.

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 21)

10

Scheme 11 depicts the preparation of 2,6-dimethylphenols incorporating a phosphonate group linked to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected bromo-substituted 2,6-dimethylphenol 11.1 is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate 11.2. The
15 coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product 11.3 is converted, using the procedures described
20 above, (Scheme 9) into the corresponding phenoxyacetic acid 11.4. Alternatively, the olefinic product 11.3 is reduced to afford the saturated 2,6-dimethylphenol derivative 11.5. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or
25 diimide. Following the reduction reaction, the product 11.5 is converted, as described above, (Scheme 9) into the corresponding phenoxyacetic acid 11.6.

For example, 3-bromo-2,6-dimethylphenol 11.7, prepared as described in Can. J. Chem., 1983, 61, 1045, is converted into the tert-butyldimethylsilyl ether 11.8, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective
30 Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product 11.8 is reacted with an equimolar amount of a dialkyl allyl phosphonate 11.9, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of

bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°, to produce the coupled product 11.10. The silyl group is removed, for example by the treatment of the ether 11.10 with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol 11.11. This compound is converted, employing the procedures described above, (Scheme 9) into the corresponding phenoxyacetic acid 11.12. Alternatively, the unsaturated compound 11.11 is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog 11.13. This compound is converted, employing the procedures described above, (Scheme 9) into the corresponding phenoxyacetic acid 11.14.

Using the above procedures, but employing, in place of 3-bromo-2,6-dimethylphenol 11.7, different bromophenols 11.1, and/or different dialkyl alkenyl phosphonates 11.2, the corresponding products 11.4 and 11.6 are obtained.

Scheme 12 illustrates the preparation of phosphonate-containing 2,6-dimethylphenoxyacetic acids 12.1 in which the phosphonate group is attached to the 2,6-dimethylphenoxy moiety by means of a carbocyclic ring. In this procedure, a bromo-substituted 2,6-dimethylphenol 12.2 is converted, using the procedures illustrated in Scheme 9, into the corresponding 2,6-dimethylphenoxyacetic ester 12.3. The latter compound is then reacted, by means of a palladium-catalyzed Heck reaction, with a cycloalkenone 12.4, in which n is 1 or 2. The coupling reaction is conducted under the same conditions as those described above for the preparation of 11.3. (Scheme 11). The product 12.5 is then reduced catalytically, as described above for the reduction of 11.3, (Scheme 11), to afford the substituted cycloalkanone 12.6. The ketone is then subjected to a reductive amination procedure, by reaction with a dialkyl 2-aminoethylphosphonate 12.7 and sodium triacetoxyborohydride, as described in J. Org. Chem., 61, 3849, 1996, to yield the amine phosphonate 12.8. The reductive amination reaction is conducted under the same conditions as those described above for the preparation of the amine 10.3 (Scheme 10). The resultant ester 12.8 is then hydrolyzed, as described above, to afford the phenoxyacetic acid 12.1.

For example, 4-bromo-2,6-dimethylphenol 12.9 (Aldrich) is converted, as described above, into the phenoxy ester 12.10. The latter compound is then coupled, in dimethylformamide

solution at ca. 60°, with cyclohexenone 12.11, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to yield the cyclohexenone 12.12. The enone is then reduced to the saturated ketone 12.13, by means of catalytic hydrogenation employing 5% palladium on carbon as catalyst. The saturated ketone is then reacted with an equimolar amount of a dialkyl aminoethylphosphonate 12.14, prepared as described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the amine 12.15. Hydrolysis, employing lithium hydroxide in aqueous methanol at ambient temperature, then yields the acetic acid 12.16.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylphenol 12.9, different bromo-substituted 2,6-dimethylphenols 12.2, and/or different cycloalkenones 12.4, and/or different dialkyl aminoalkylphosphonates 12.7, the corresponding products 12.1 are obtained.

Scheme 13 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate group attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an optionally protected hydroxy, thio or amino-substituted 2,6-dimethylphenol 13.1 is reacted, in the presence of a base such as, for example, potassium carbonate, and optionally in the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate 13.2. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°. The product of the alkylation reaction, 13.3 is then converted, as described above (Scheme 9) into the phenoxyacetic acid 13.4.

For example, 2,6-dimethyl-4-mercaptophenol 13.5, prepared as described in EP 482342, is reacted in dimethylformamide at ca. 60° with an equimolar amount of a dialkyl bromobutyl phosphonate 13.6, the preparation of which is described in Synthesis, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the thioether product 13.7. This compound is converted, employing the procedures described above, (Scheme 9) into the corresponding phenoxyacetic acid 13.8.

Using the above procedures, but employing, in place of 2,6-dimethyl-4-mercaptophenol 13.5, different hydroxy, thio or aminophenols 13.1, and/or different dialkyl bromoalkyl phosphonates 13.2, the corresponding products 13.4 are obtained.

Scheme 14 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester group attached by means of an aromatic or heteroaromatic group. In this procedure, an optionally protected hydroxy, mercapto or amino-substituted 2,6-

5 dimethylphenol 14.1 is reacted, under basic conditions, with a bis(halomethyl)aryl or heteroaryl compound 14.2. Equimolar amounts of the phenol and the halomethyl compound are reacted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium or cesium carbonate, or dimethylaminopyridine, to afford the ether, thioether or amino product 14.3. The product 14.3 is then converted, using the

10 procedures described above, (Scheme 9) into the phenoxyacetic ester 14.4. The latter compound is then subjected to an Arbuzov reaction by reaction with a trialkylphosphite 14.5 at ca. 100° to afford the phosphonate ester 14.6. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992, 115. The resultant product 14.6 is then converted into the acetic acid 14.7 by hydrolysis of the

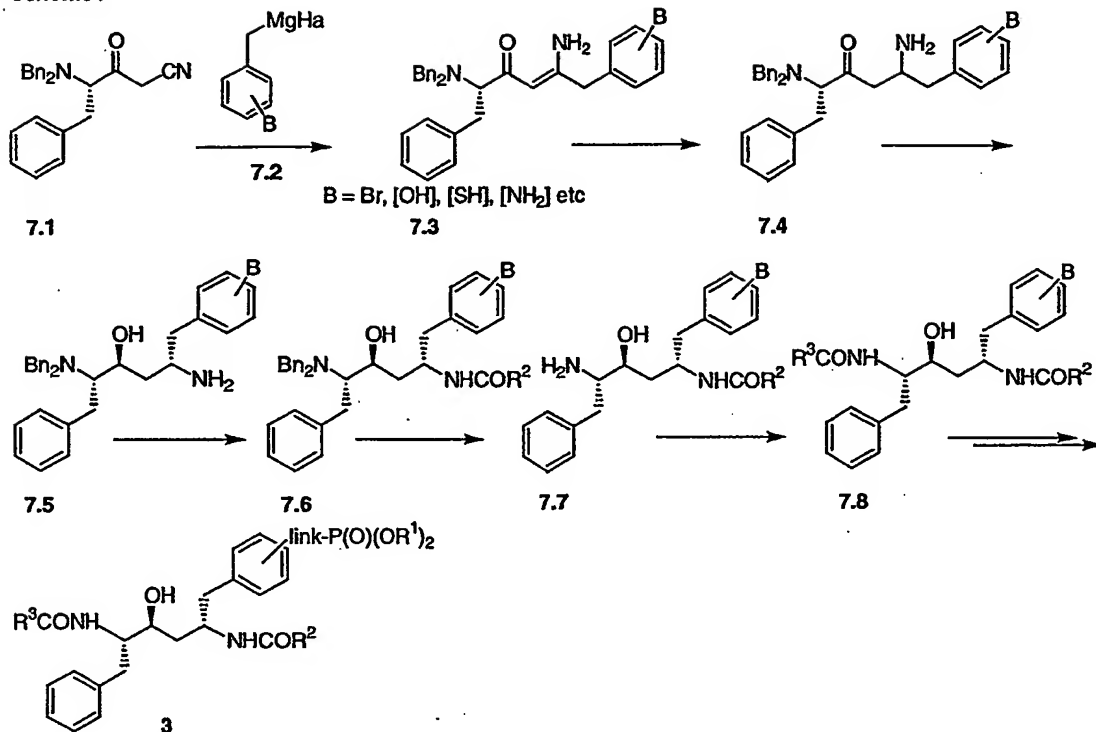
15 ester moiety, using the procedures described above, (Scheme 9).

For example, 4-hydroxy-2,6-dimethylphenol 14.8 (Aldrich) is reacted with one molar equivalent of 3,5-bis(chloromethyl)pyridine, the preparation of which is described in Eur. J. Inorg. Chem., 1998, 2, 163, to afford the ether 14.10. The reaction is conducted in acetonitrile at ambient temperature in the presence of five molar equivalents of potassium carbonate. The

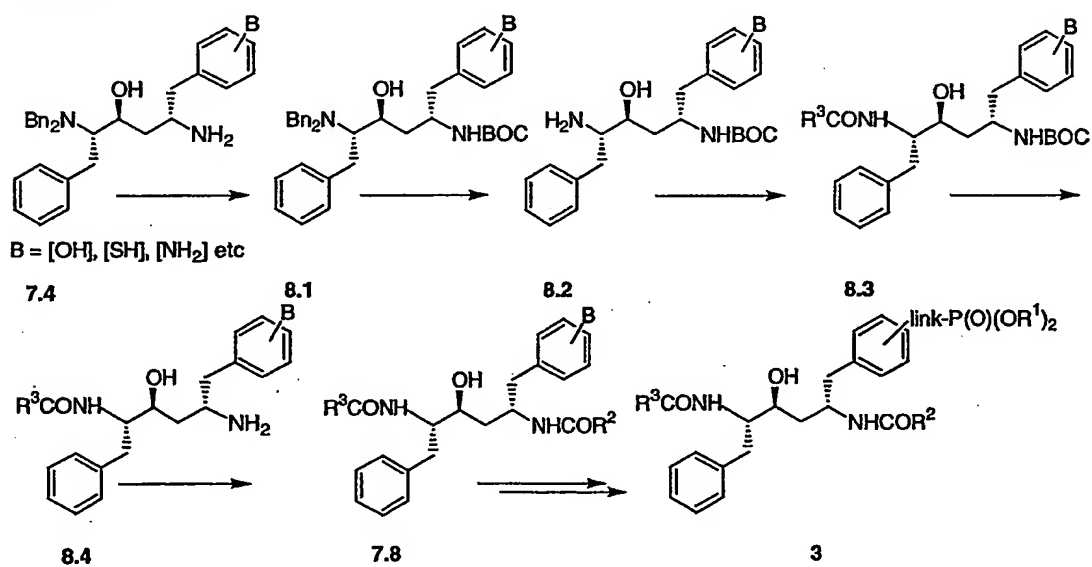
20 product 14.10 is then reacted with ethyl bromoacetate, using the procedures described above, (Scheme 9) to afford the phenoxyacetic ester 14.11. This product is heated at 100° for 3 hours with three molar equivalents of triethyl phosphite 14.12, to afford the phosphonate ester 14.13. Hydrolysis of the acetic ester moiety, as described above, for example by reaction with lithium hydroxide in aqueous ethanol, then affords the phenoxyacetic acid 14.14.

25 Using the above procedures, but employing, in place of the bis(chloromethyl) pyridine 14.9, different bis(halomethyl) aromatic or heteroaromatic compounds 14.2, and/or different hydroxy, mercapto or amino-substituted 2,6-dimethylphenols 14.1 and/or different trialkyl phosphites 14.5, the corresponding products 14.7 are obtained.

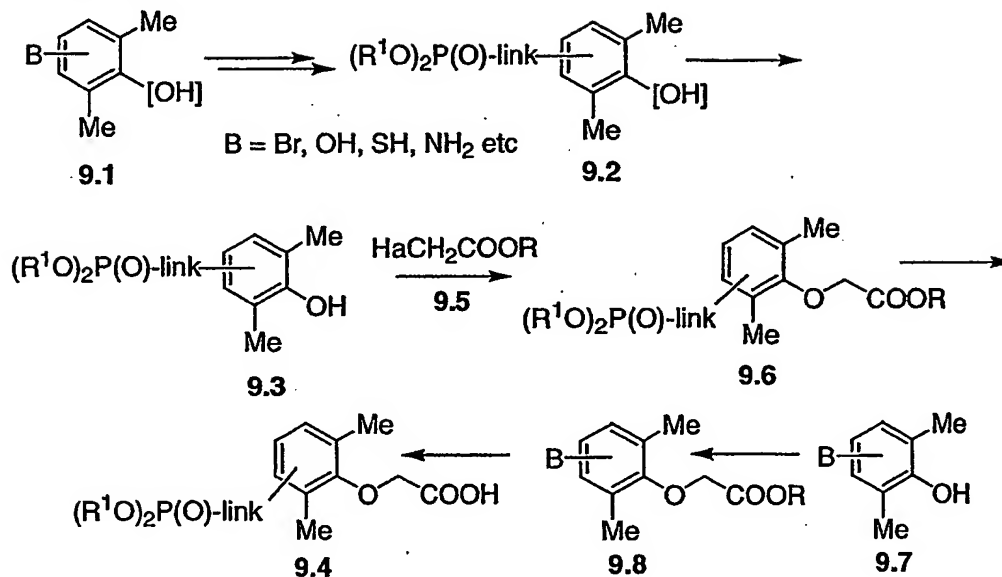
Scheme 7



Scheme 8

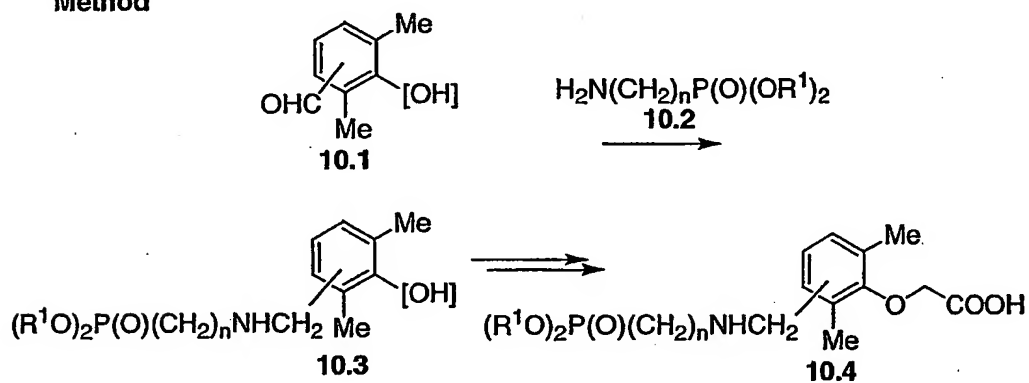


Scheme 9

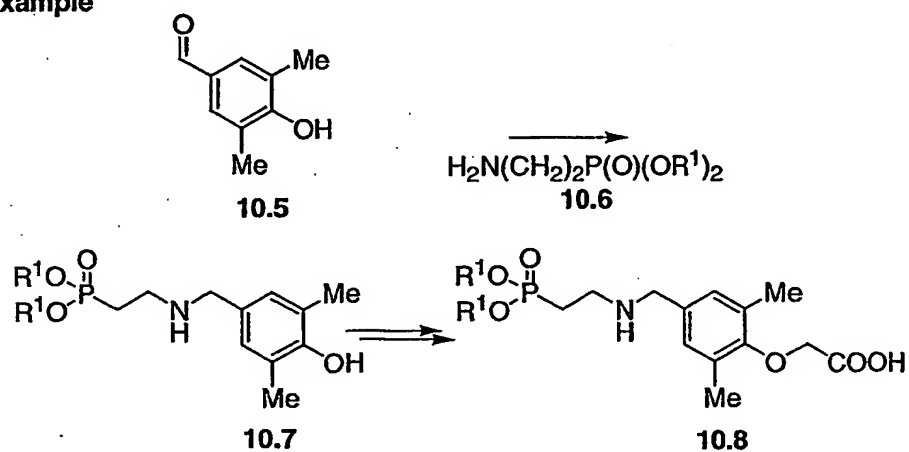


Scheme 10

Method

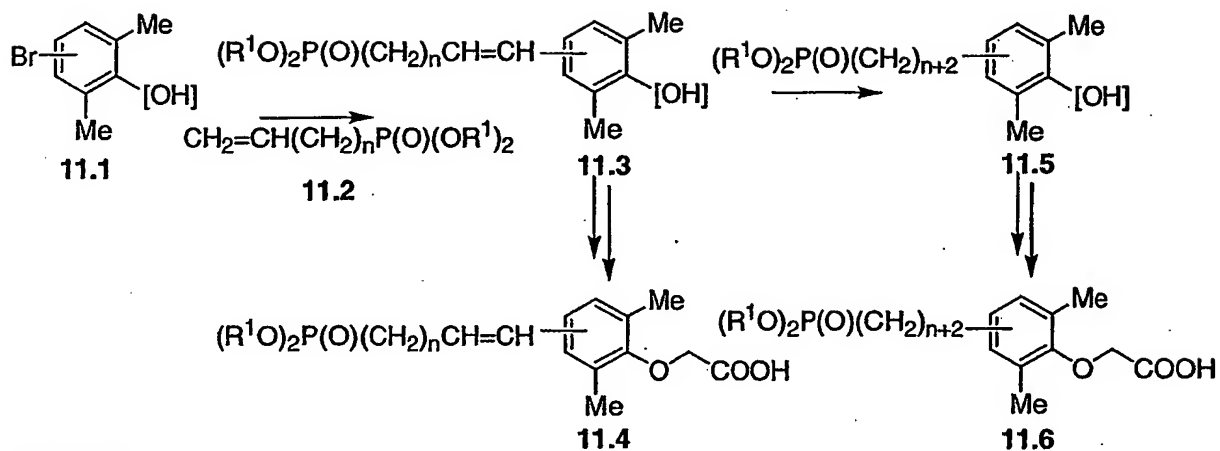


Example

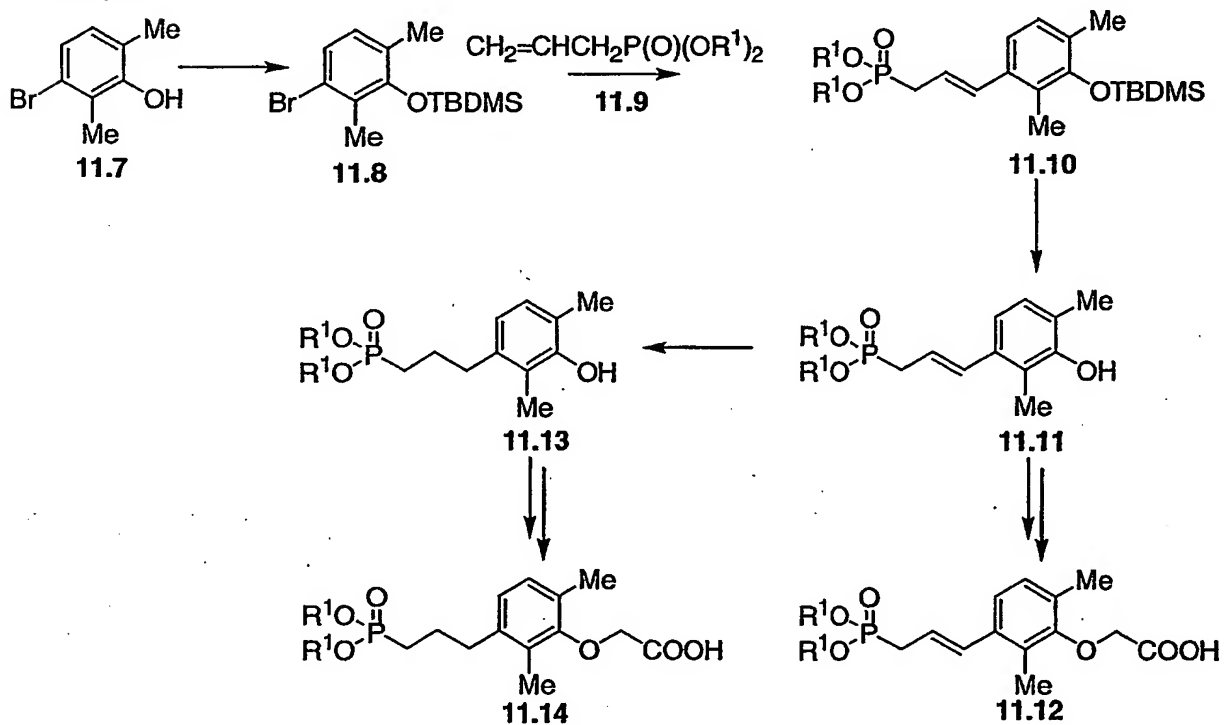


Scheme 11

Method

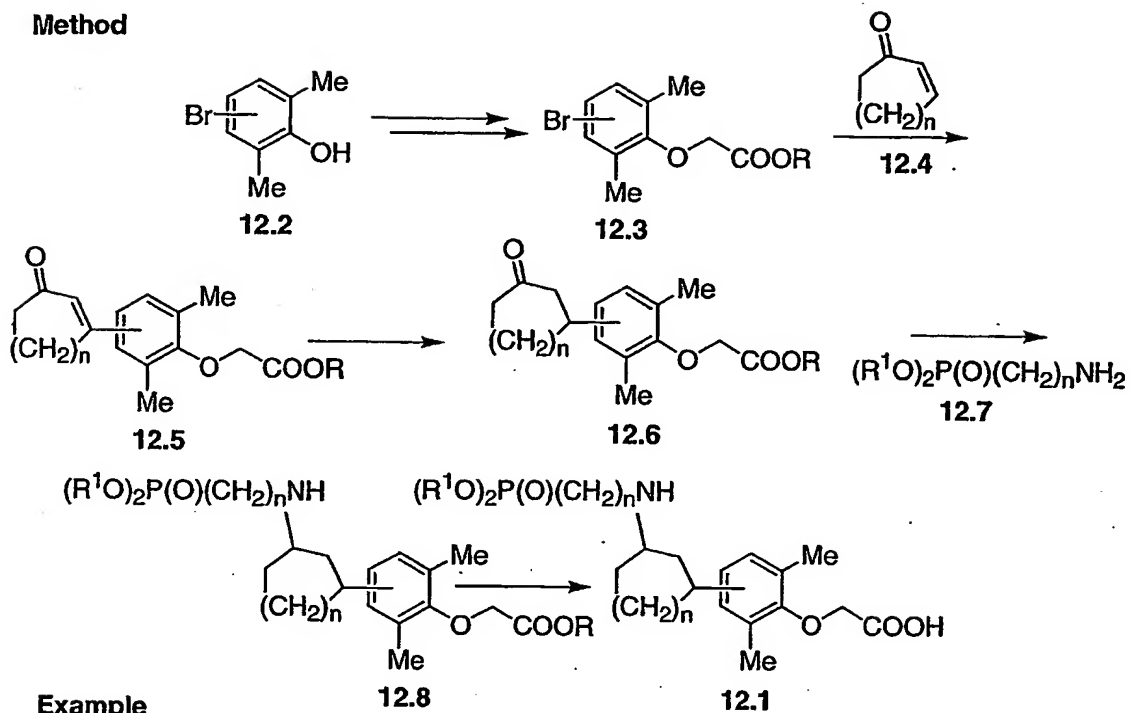


Example

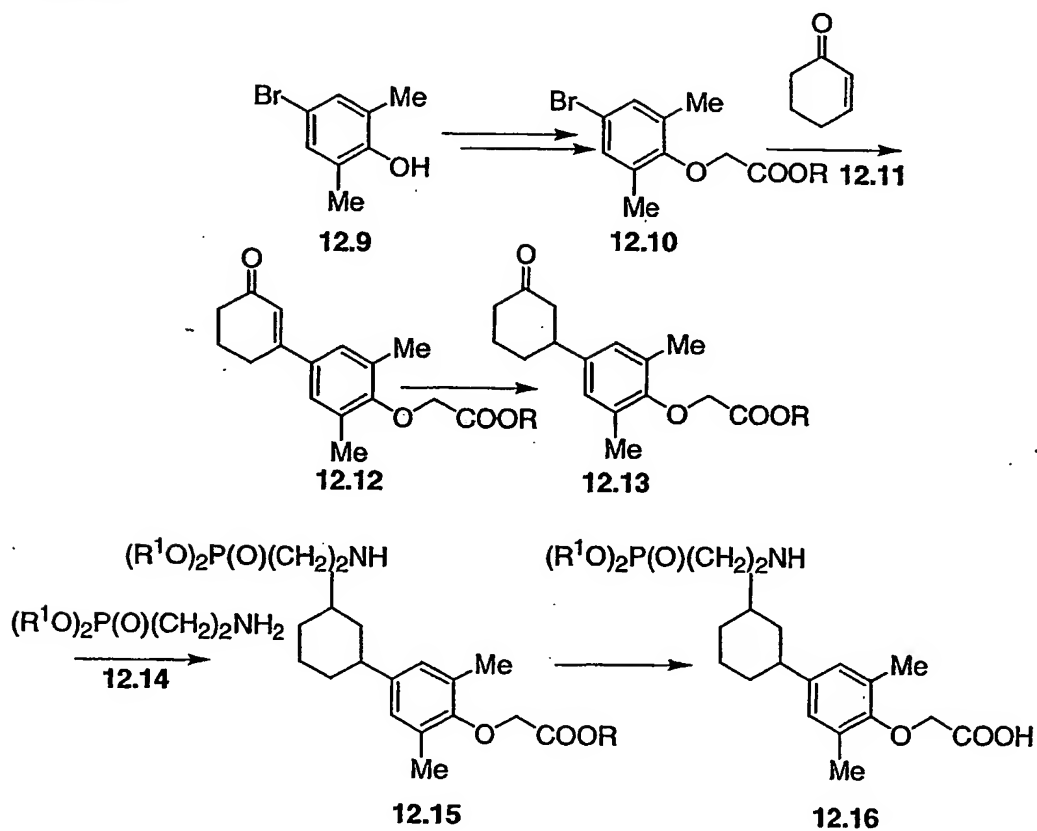


Scheme 12

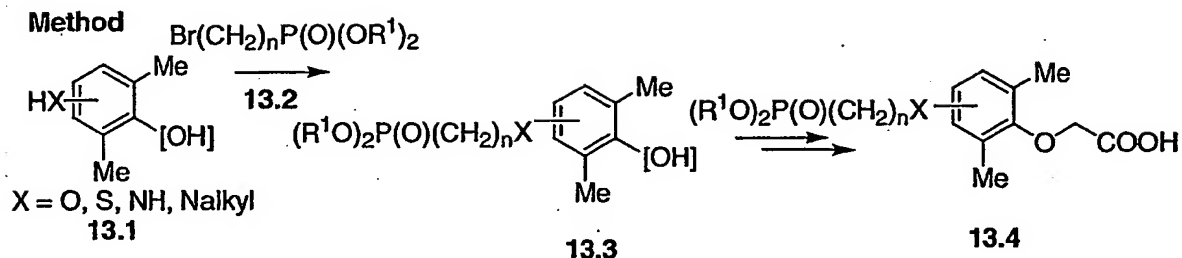
Method



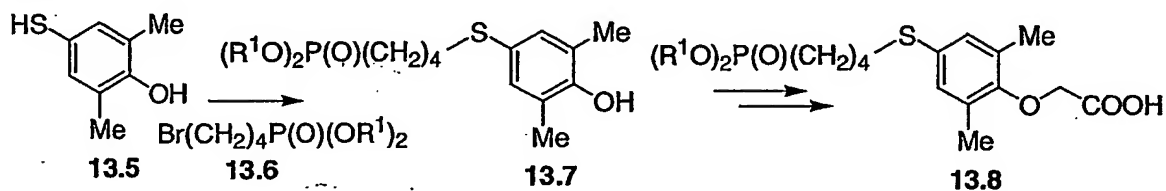
Example



Scheme 13

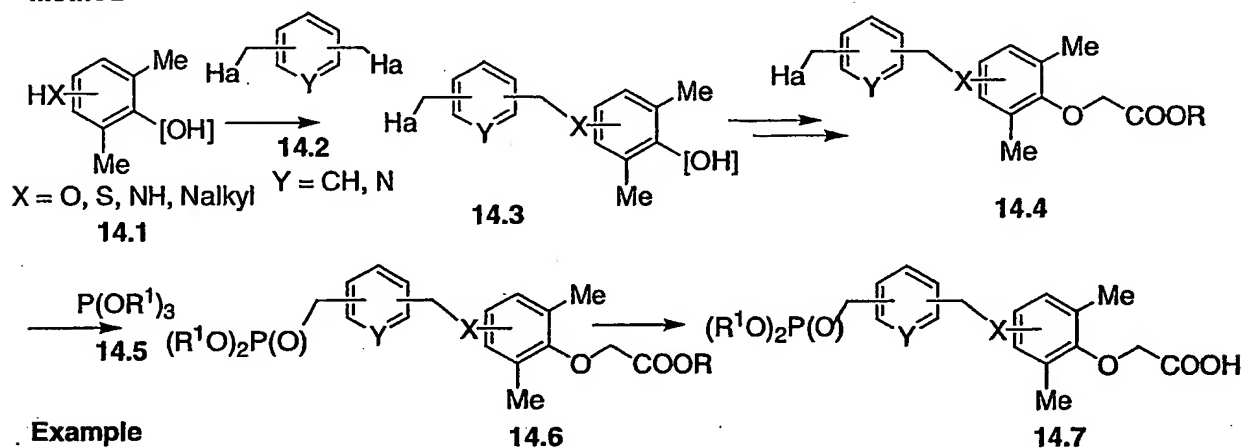


Example

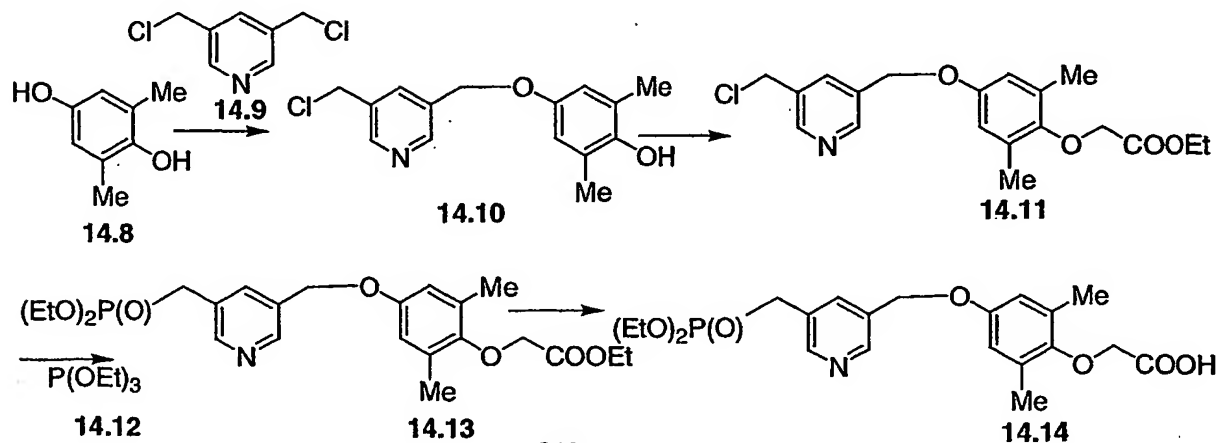


Scheme 14

Method



Example



Preparation of phenylalanine derivatives 4.1 incorporating phosphonate moieties, or precursors thereto.

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Schemes 15-17 describe various methods for the preparation of phosphonate-containing analogs of phenylalanine. The compounds are then employed, as described above, (Schemes 4 and 5) in the preparation of the compounds 2.

10

Scheme 15 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives 15.5.

15

In this procedure, a hydroxy or mercapto-substituted phenylalanine 15.1 is converted into the benzyl ester 15.2. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester 15.2 is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W.

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Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, suitable OH and SH protecting groups include tert-butyldimethylsilyl or tert-butyldiphenylsilyl.

25

Alternative SH protecting groups include 4-methoxybenzyl and S-adamantyl. The protected hydroxy- or mercapto ester 15.3 is then reacted with a benzyl or substituted benzyl halide and a base, for example as described in U.S. Patent 5,491,253, to afford the N, N-dibenzyl product 15.4. For example, the amine 15.3 is reacted at ca. 90° with two molar equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, to afford the tribenzylated product 15.4, as described in U.S. Patent 5,491,253. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in

30

Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride and the like, in a solvent such as tetrahydrofuran at ambient

temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl protecting groups are removed by treatment with mercuric trifluoroacetate in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.

The resultant phenol or thiophenol 15.5 is then reacted under various conditions to provide protected phenylalanine derivatives 15.6, 15.7 or 15.8, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

As one option, the phenol or thiophenol 15.5 is reacted with a dialkyl bromoalkyl phosphonate 15.9 to afford the product 15.6. The alkylation reaction between 15.5 and 15.9 is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate. The reaction is performed at from ambient temperature to ca. 80°, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product 15.6.

For example, as illustrated in Scheme 15 Example 1, a hydroxy-substituted phenylalanine derivative such as tyrosine, 15.12 is converted, as described above, into the benzyl ester 15.13.

The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether 15.14. This compound is then converted, as described above, into the tribenzylated derivative 15.15. The silyl protecting group is removed by treatment of 15.15 with a tetrahydrofuran solution of tetrabutylammonium fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol 15.16. The latter compound is then reacted in dimethylformamide at ca. 60°, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate 15.17 (Aldrich), in the presence of cesium carbonate, to afford the alkylated product 15.18.

Using the above procedures, but employing, in place of the 4-hydroxy phenylalanine 15.12, different hydroxy or thio-substituted phenylalanine derivatives 15.1, and/or different bromoalkyl phosphonates 15.9, the corresponding ether or thioether products 15.6 are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative 15.5 is reacted with a dialkyl hydroxymethyl phosphonate 15.10 under the conditions of the Mitsunobu reaction, to afford the ether or thioether compounds 15.7. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in

Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine.

- 5 For example, as shown in Scheme 15, Example 2, 3-mercaptophenylalanine 15.19, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester 15.20. The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether 15.21. This compound is
10 then converted, as described above for the preparation of the tribenzylated phenylalanine derivative 15.4, into the tribenzyl derivative 15.22. The 4-methoxybenzyl group is then removed by the reaction of the thioether 15.22 with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in J.Org. Chem., 52, 4420, 1987, to afford the thiol 15.23. The latter compound is reacted, under the conditions of the Mitsunobu reaction, with a
15 dialkyl hydroxymethyl phosphonate 15.24, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product 15.25. Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative 15.19, different hydroxy or mercapto-substituted phenylalanines 15.1, and/or different dialkylhydroxymethyl phosphonates 15.10, the corresponding products 15.7
20 are obtained.

- Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative 15.5 is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate 15.11 in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base
25 such as triethylamine or cesium carbonate, to afford the ether or thioether products 15.8. For example, as illustrated in Scheme 15, Example 3, 3-hydroxyphenylalanine 15.26 (Fluka) is converted, using the procedures described above, into the tribenzylated compound 15.27. The latter compound is reacted, in dimethylformamide at ca. 50°, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate 15.28, prepared as
30 described in Tet. Lett., 1986, 27, 1477, to afford the ether product 15.29. Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative 15.26, different hydroxy or mercapto-substituted phenylalanines 15.1, and/or

different dialkyl trifluoromethanesulfonyloxymethylphosphonates 15.11, the corresponding products 15.8 are obtained.

Scheme 16 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted tribenzylated phenylalanine derivative 16.1 and a dialkyl aminoalkylphosphonate 16.2.

In this procedure, a hydroxymethyl-substituted phenylalanine 16.3 is converted into the tribenzylated derivative 16.4 by reaction with three equivalents of a benzyl halide, for example, benzyl chloride, in the presence of an organic or inorganic base such as diazabicyclononene or potassium carbonate. The reaction is conducted in a polar solvent optionally in the additional presence of water. For example, the aminoacid 16.3 is reacted with three equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, as described in U.S. Patent 5,491,253, to afford the product 16.4. The latter compound is then oxidized to afford the corresponding aldehyde 16.1. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product 16.1. For example, the carbinol 16.4 is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in J. Org. Chem., 43, 2480, 1978, to yield the aldehyde 16.1. This compound is reacted with a dialkyl aminoalkylphosphonate 16.2 in the presence of a suitable reducing agent to afford the amine product 16.5. The preparation of amines by means of a reductive amination reaction is described above (Scheme 10). For example, 3-(hydroxymethyl)-phenylalanine 16.6, prepared as described in Acta Chem. Scand. Ser. B, 1977, B31, 109, is converted, as described above, into the formylated derivative 16.8. This compound is then reacted, in ethanol, at ambient temperature, with one molar equivalent of a dialkyl aminoethylphosphonate 16.9, prepared as described in J. Org. Chem., 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product 16.10.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine 16.6, different hydroxymethyl phenylalanines 16.3, and/or different aminoalkyl phosphonates 16.2, the corresponding products 16.5 are obtained.

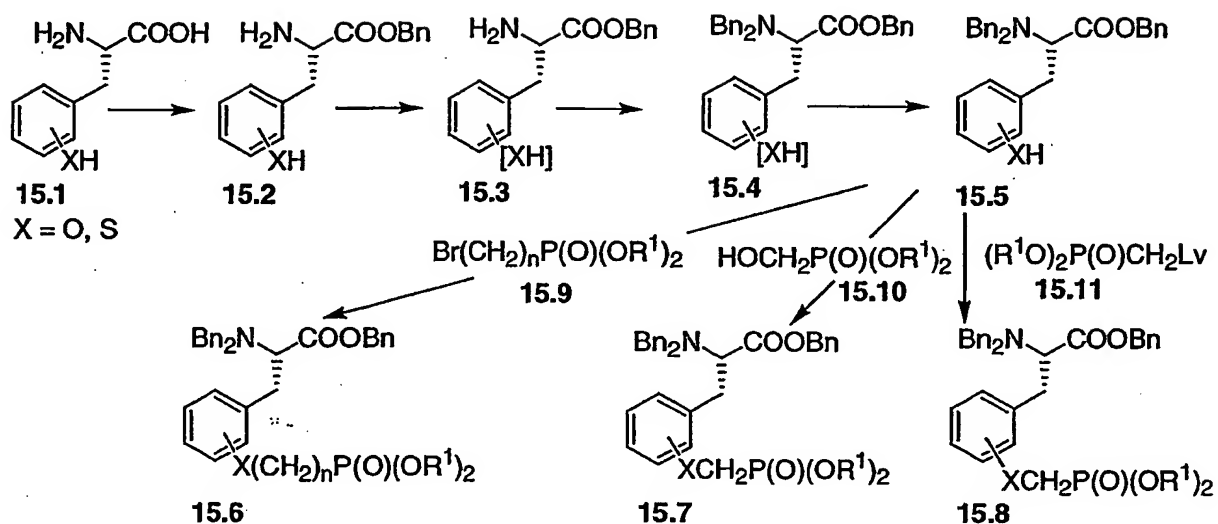
- 5 Scheme 17 depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a suitably protected bromo-substituted phenylalanine 17.2 is coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite 17.3 to produce the phosphonate ester 17.4. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.

- 10 For example, 3-bromophenylalanine 17.5, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme 15) into the tribenzylated compound 17.6. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite 17.7, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 17.8.

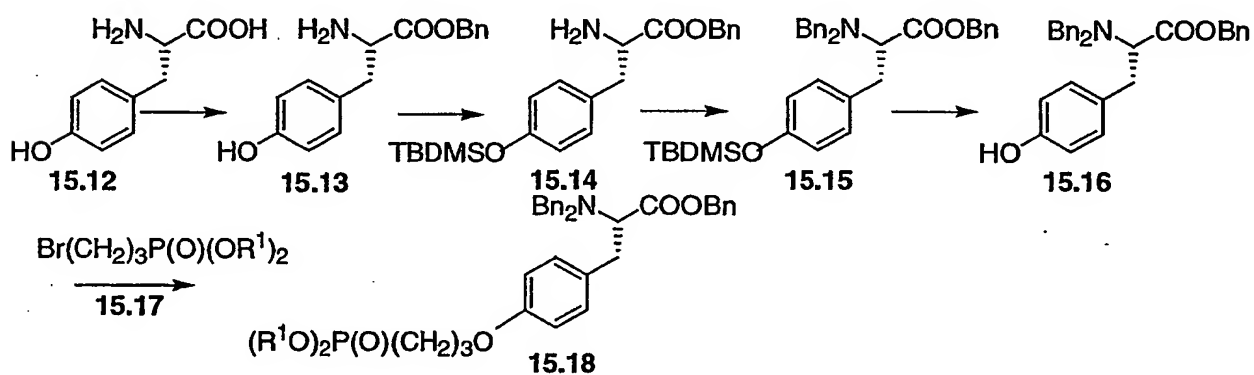
Using the above procedures, but employing, in place of 3-bromophenylalanine 17.5, different bromophenylalanines 17.1, and/or different dialkylphosphites 17.3, the corresponding products 17.4 are obtained.

Scheme 15

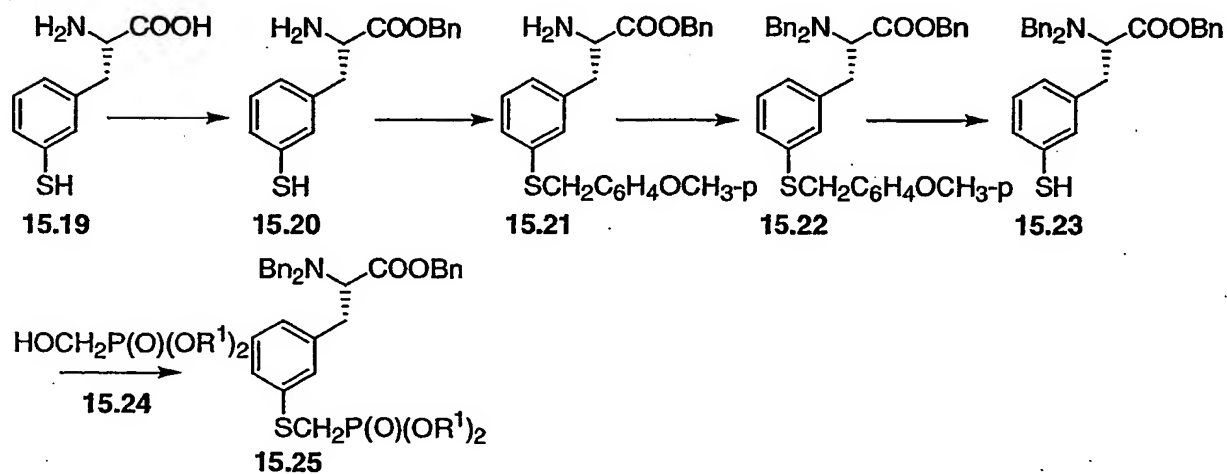
Method



Example 1

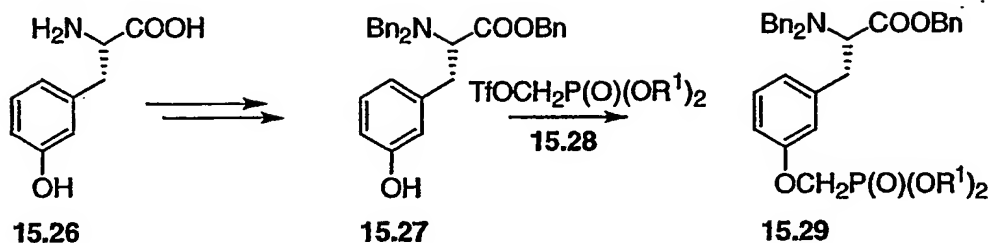


Example 2



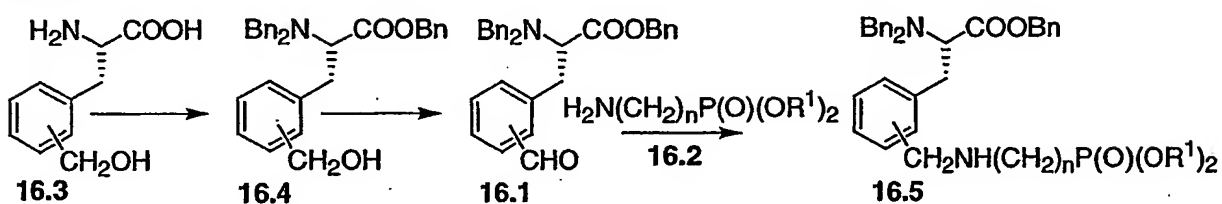
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Example 3

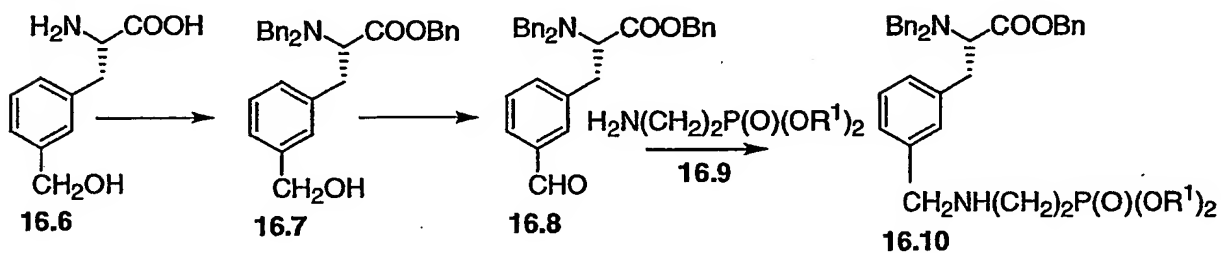


Scheme 16

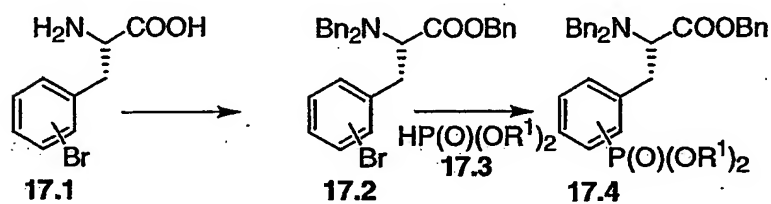
Method



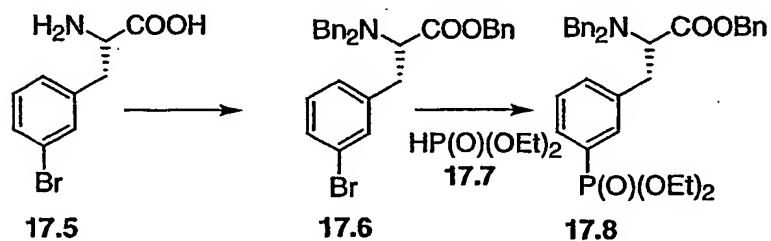
Example



Scheme 17



Example



Preparation of phosphonate esters with structure 3.

Scheme 18 illustrates the preparation of compounds 3 in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, the ketonitrile 7.1, prepared as described in J. Org. Chem., 1994, 59, 4080, is reacted, as described above (Scheme n) with a bromobenzylmagnesium halide reagent 18.1. The resultant ketoenamine 18.2 is then converted into the diacylated bromophenyl carbinol 18.3. The conditions required for the conversion of the ketoenamine 18.2 into the carbinol 18.3 are similar to those described above (Scheme 7), for the conversion of the ketoenamine 7.3 into the carbinol 7.8. The product 18.3 is then reacted with a dialkyl phosphite 17.3, in the presence of a palladium (0) catalyst, to yield the phosphonate ester 3. The conditions for the coupling reaction are the same as those described above (Scheme 17) for the preparation of the phosphonate ester 17.8.

For example, the ketonitrile 7.1 is reacted, in tetrahydrofuran solution at 0°, with three molar equivalents of 4-bromobenzylmagnesium bromide 18.4, the preparation of which is described in Tetrahedron, 2000, 56, 10067, to afford the ketoenamine 18.5. The latter compound is then converted into the diacylated bromophenyl carbinol 18.6, using the sequence of reactions described above (Scheme 7) for the conversion of the ketoenamine 7.3 into the carbinol 7.8. The resultant bromo compound 18.6 is then reacted with diethyl phosphite 18.7 and triethylamine, in toluene solution at reflux, in the presence of tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 18.8.

Using the above procedures, but employing, in place of 4-bromobenzylmagnesium bromide 18.4, different bromobenzylmagnesium halides 18.1 and/or different dialkyl phosphites 17.3, there are obtained the corresponding phosphonate esters 3.

Scheme 19 illustrates the preparation of compounds 3 in which the phosphonate ester moiety is attached to the nucleus by means of a phenyl ring. In this procedure, a bromophenyl-substituted benzylmagnesium bromide 19.1, prepared from the corresponding bromomethyl compound by reaction with magnesium, is reacted with the ketonitrile 7.1. The conditions for this transformation are the same as those described above (Scheme 7). The product of the Grignard addition reaction is then transformed, using the sequence of reactions described

above, (Scheme 7) into the diacylated carbinol 19.2. The latter compound is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite 17.3, to afford the phenylphosphonate 3. The procedure for the coupling reaction is the same as those described above for the preparation of the phosphonate 17.4.

- 5 For example, 4-(4-bromophenyl)benzyl bromide, prepared as described in DE 2262340, is reacted with magnesium to afford 4-(4-bromophenyl)benzylmagnesium bromide 19.3. This product is then reacted with the ketonitrile 7.1, as described above, to yield, after the sequence of reactions shown in Scheme 7, the diacylated carbinol 19.4. The latter compound is then reacted, as described above, (Scheme 17) with a diethyl phosphite 17.3, to afford the
10 phenylphosphonate 19.5.

Using the above procedures, but employing, in place of 4-(4-bromophenyl)benzyl bromide 19.3, different bromophenylbenzyl bromides 19.1, and/or different dialkyl phosphites 17.3, the corresponding products 3 are obtained.

- 15 Scheme 20 depicts the preparation of phosphonate esters 3 in which the phosphonate group is attached by means of a heteroatom and a methylene group. In this procedure, a hetero-substituted benzyl alcohol 20.1 is protected, affording the derivative 20.2. The protection of phenyl hydroxyl, thiol and amino groups are described, respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p.
20 277, 309. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, as
25 described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. Amino groups can be protected, for example by dibenzylation. The conversion of amines into dibenzylamines, for example by treatment with benzyl bromide in a polar solvent such as acetonitrile or aqueous ethanol, in the presence of a base such as triethylamine or sodium carbonate, is described in Protective Groups in Organic Synthesis, by
30 T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 364. The resultant protected benzyl alcohol 20.2 is converted into a halo derivative 20.3, in which Ha is chloro or bromo. The conversion of alcohols into chlorides and bromides is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. For example, benzyl alcohols **20.2** can be transformed into the chloro compounds **20.3**, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols can be transformed into
5 bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. The resultant protected benzyl halide **20.3** is then converted into the corresponding benzylmagnesium halide **20.4** by reaction with magnesium metal in an ethereal solvent, or by a Grignard exchange reaction treatment with an alkyl magnesium halide. The resultant substituted benzylmagnesium halide **20.4** is then converted,
10 using the sequence of reactions described above (Scheme 7) for the preparation of **7.8**, into the carbinol **20.5** in which the substituent XH is suitably protected.

The protecting group is then removed to afford the phenol, thiophenol or amine **20.6**.

Deprotection of phenols, thiophenols and amines is described respectively in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990.

15 For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am. Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperature, as described in Chem. Pharm. Bull., 26, 1576, 1978. N,N-dibenzyl
20 amines can be converted into the unprotected amines by catalytic reduction in the presence of a palladium catalyst, as described above (Scheme 1). The resultant phenol, thiophenol or amine **20.6** is then converted into the phosphonate ester **3** by reaction with an activated derivative of a dialkyl hydroxymethyl phosphonate **15.11**, in which Lv is a leaving group. The reaction is conducted under the same conditions as described above for the alkylation of the
25 phenol **15.5** to afford the ether or thioether **15.8** (Scheme 15).

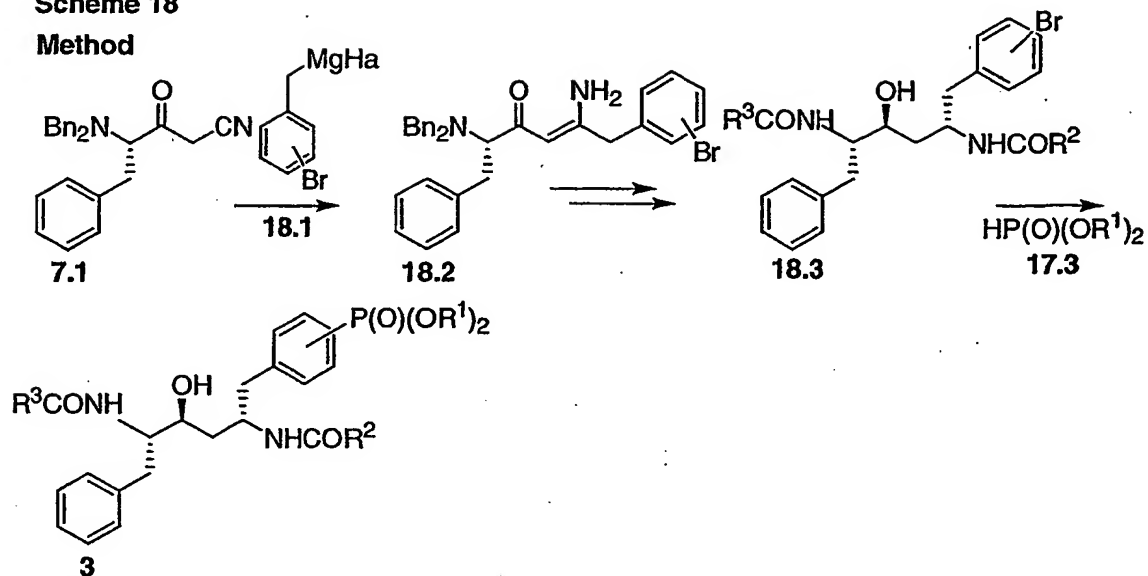
For example, 3-hydroxybenzyl alcohol **20.7** (Aldrich) is reacted with chlorotriisopropylsilane and imidazole in dimethylformamide, as described in Tet. Lett., 2865, 1964, to afford the silyl ether **20.8**. This compound is reacted with carbon tetrabromide and triphenylphosphine in dichloromethane, as described in J. Am. Chem. Soc., 109, 2738, 1987, to afford the
30 brominated product **20.9**. This material is reacted with magnesium in ether to afford the Grignard reagent **20.10**, which is then subjected to the series of reaction shown in Scheme 7 to afford the carbinol **20.11**. The triisopropylsilyl protecting group is then removed by treatment

of the ether **20.11** with tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Org. Chem., 51, 4941, 1986. The resultant phenol **20.12** is then reacted in dimethylformamide solution with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **15.28**, prepared as described in Synthesis, 4, 327, 1998, in the presence of a base such as dimethylaminopyridine, as described above (Scheme 15) to afford the phosphonate product **20.13**.

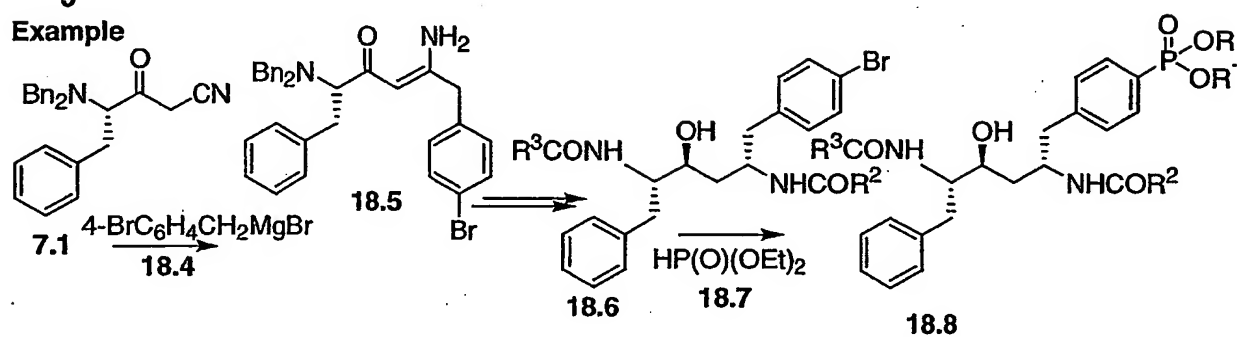
5 Using the above procedures, but employing, in place of 3-hydroxybenzyl alcohol **20.7**, different hydroxy, mercapto or amino-substituted benzyl alcohols **20.1**, and/or different dialkyl hydroxymethyl phosphonate derivatives **15.11**, the corresponding products **3** are obtained.

Scheme 18

Method

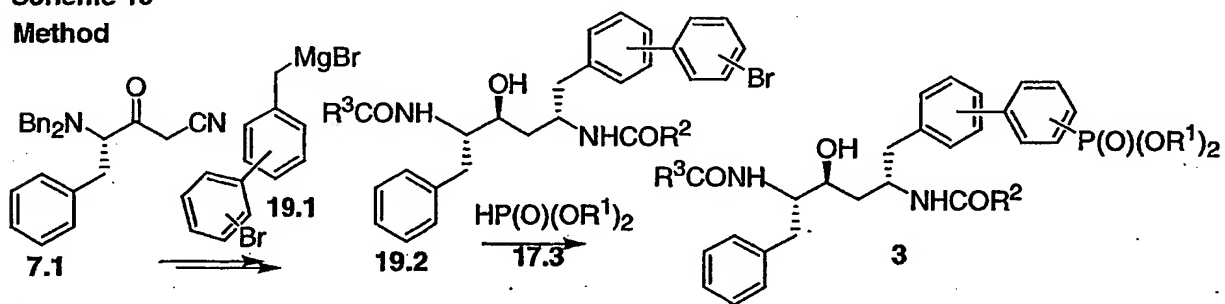


Example

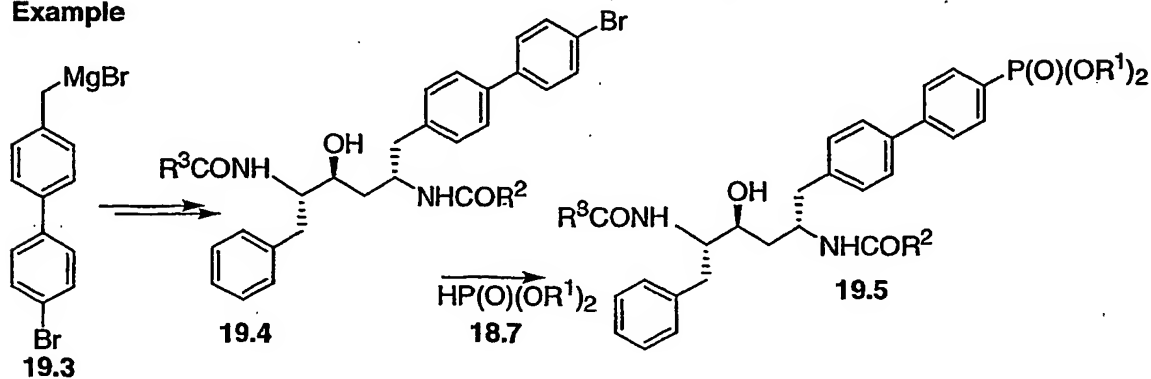


Scheme 19

Method

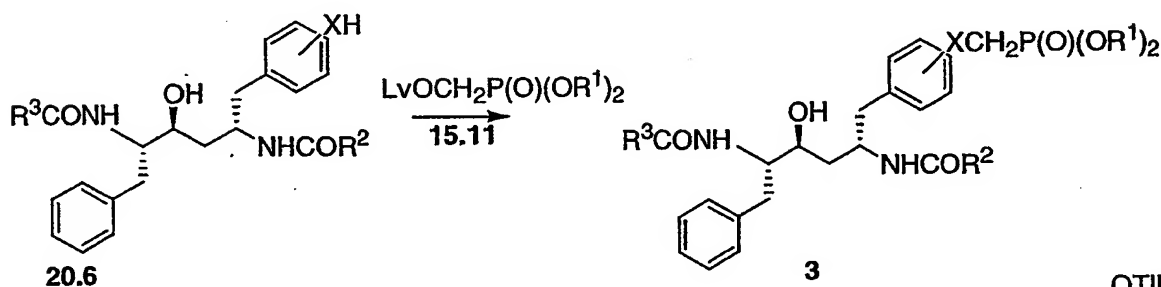
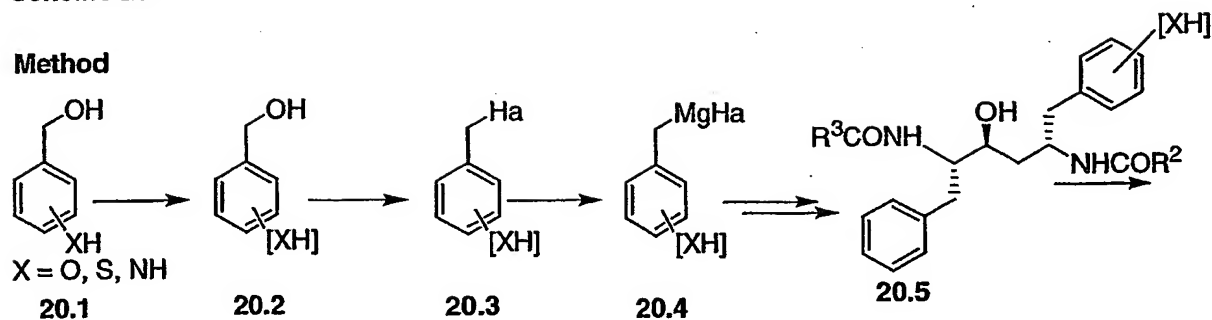


Example

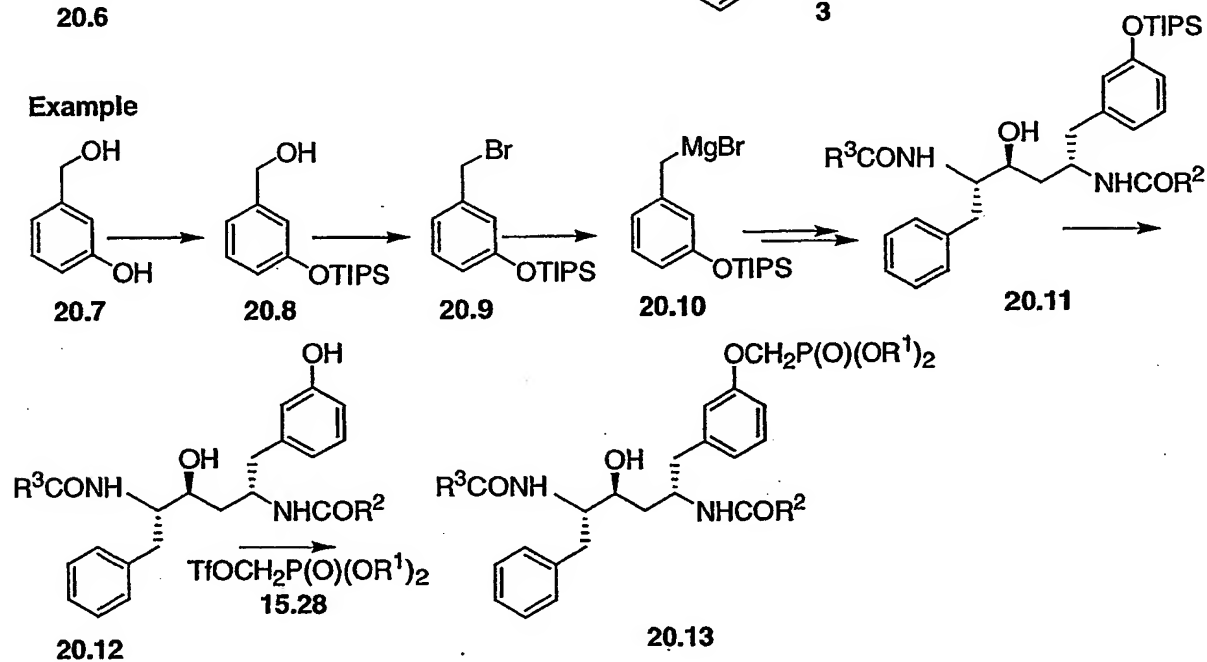


Scheme 20

Method



Example



Schemes 1-33 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may be the same or different. The R¹ groups attached to a phosphonate esters 1-5, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 21. The group R in Scheme 21 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1-5 or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-5. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 21.1 into the corresponding phosphonate monoester 21.2 (Scheme 21, Reaction 1) can be accomplished by a number of methods. For example, the ester 21.1 in which R¹ is an aralkyl group such as benzyl, can be converted into the monoester compound 21.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester 21.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 21.2 can be effected by treatment of the ester 21.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

Phosphonate diesters 21.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 21.2 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, can be converted into the monoester 21.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 21.1 or a phosphonate monoester 21.2 into the corresponding phosphonic acid 21.3 (Scheme 21, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc.,

Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 21.2 in which R¹ is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid 21.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an etheral solvent such as dioxan. A phosphonate monoester 21.2 in which R¹ is alkenyl such as, for example, allyl, can be converted into the phosphonic acid 21.3 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters 21.1 in which R¹ is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters 21.1 in which R¹ is phenyl is described in J. Amer. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester 21.2 into a phosphonate diester 21.1 (Scheme 21, Reaction 4) in which the newly introduced R¹ group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate 21.2 is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester 21.2 to the diester 21.1 can be effected by the use of the Mitsunobu reaction, as described above (Scheme 15). The substrate is reacted with the hydroxy compound R¹OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester 21.2 can be transformed into the phosphonate diester 21.1, in which the introduced R¹ group is alkenyl or aralkyl, by reaction of the monoester with the halide R¹Br, in which R¹ is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as

cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester 21.2 is transformed into the chloro analog $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M.

- 5 Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester 21.1.

- A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ can be transformed into a phosphonate monoester $\text{RP}(\text{O})(\text{OR}^1)(\text{OH})$ (Scheme 21, Reaction 5) by means of the methods described above of for
10 the preparation of the phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ 21.1, except that only one molar proportion of the component R^1OH or R^1Br is employed.

- A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ 21.3 can be transformed into a phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ 21.1 (Scheme 21, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and
15 triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids 21.3 can be transformed into phosphonic esters 21.1 in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70° . Alternatively, phosphonic acids 21.3 can be transformed into phosphonic esters 21.1 in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is
20 reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester 21.1.

Phosphonate esters 1-5 incorporating carbamate moieties.

- 25 The phosphonate esters 1-5 in which the R^2CO or R^3CO groups are formally derived from the carboxylic acid synthons C38 - C49 as shown in Chart 2c, contain a carbamate moiety. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p.
30 260ff.

Scheme 22 illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme 22, in the general reaction generating carbamates, a carbinol 22.1 is converted into the activated derivative 22.2 in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative 22.2 is then reacted with an amine 22.3, to afford the carbamate product 22.4. Examples 1 - 7 in Scheme 22 depict methods by which the general reaction can be effected. Examples 8 - 10 illustrate alternative methods for the preparation of carbamates.

Scheme 22, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol 22.5. In this procedure, the carbinol 22.5 is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate 22.6. The latter compound is then reacted with the amine component 22.3, in the presence of an organic or inorganic base, to afford the carbamate 22.7. For example, the chloroformyl compound 22.6 is reacted with the amine 22.3 in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate 22.7. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 22, Example 2 depicts the reaction of the chloroformate compound 22.6 with imidazole, 22.7, to produce the imidazolide 22.8. The imidazolide product is then reacted with the amine 22.3 to yield the carbamate 22.7. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 22 Example 3, depicts the reaction of the chloroformate 22.6 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 22.10. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 22.19 - 22.24 shown in Scheme 22, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 22.19, N-hydroxysuccinimide 22.20, or pentachlorophenol, 22.21, the mixed carbonate 22.10 is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of

dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 22.22 or 2-hydroxypyridine 22.23 can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

5 Scheme 22 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 22.8 is employed. In this procedure, a carbinol 22.5 is reacted with an equimolar amount of carbonyl diimidazole 22.11 to prepare the intermediate 22.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 22.8 is then reacted with an equimolar amount of the
10 amine R'NH₂ to afford the carbamate 22.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 22.7.

Scheme 22, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxy carbonyl benzotriazole 22.13. In this procedure, a carbinol ROH is reacted at ambient
15 temperature with an equimolar amount of benzotriazole carbonyl chloride 22.12, to afford the alkoxy carbonyl product 22.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine R'NH₂ to afford the carbamate 22.7. The reaction is conducted in toluene or ethanol, at from ambient temperature
20 to about 80° as described in Syn., 1977, 704.

Scheme 22, Example 6 illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, 22.14, is reacted with a carbinol 22.5 to afford the intermediate alkyloxycarbonyl intermediate 22.15. The latter reagent is then reacted with the amine R'NH₂ to afford the carbamate 22.7. The procedure in which the reagent 22.15 is derived from
25 hydroxybenzotriazole 22.19 is described in Synthesis, 1993, 908; the procedure in which the reagent 22.15 is derived from N-hydroxysuccinimide 22.20 is described in Tet. Lett., 1992, 2781; the procedure in which the reagent 22.15 is derived from 2-hydroxypyridine 22.23 is described in Tet. Lett., 1991, 4251; the procedure in which the reagent 22.15 is derived from 4-nitrophenol 22.24 is described in Syn. 1993, 103. The reaction between equimolar amounts
30 of the carbinol ROH and the carbonate 22.14 is conducted in an inert organic solvent at ambient temperature.

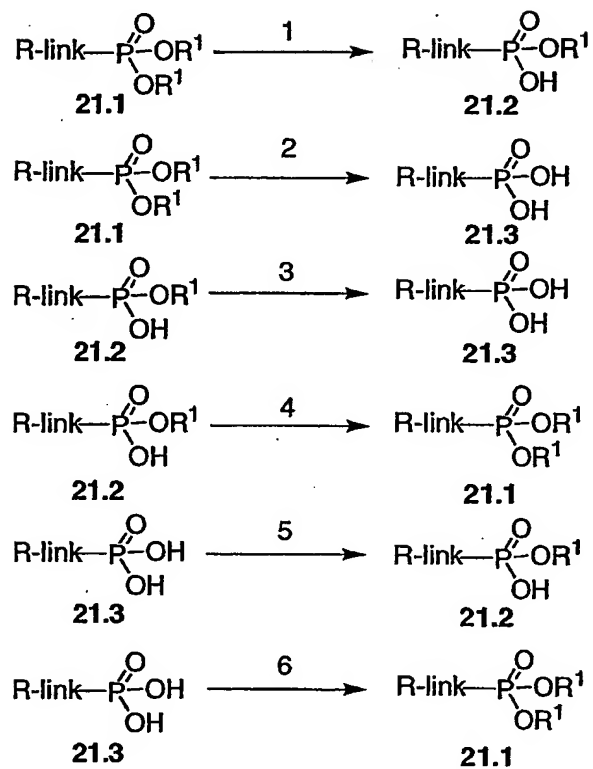
Scheme 22, Example 7 illustrates the preparation of carbamates from alkoxycarbonyl azides 22.16. in this procedure, an alkyl chloroformate 22.6 is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide 22.16. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 22.7. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme 22, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate 22.7.

Scheme 22, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate 22.18. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate 22.7.

Scheme 22, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate 22.7.

Scheme 21

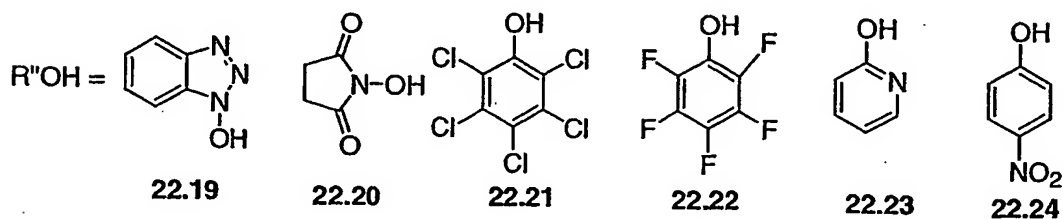
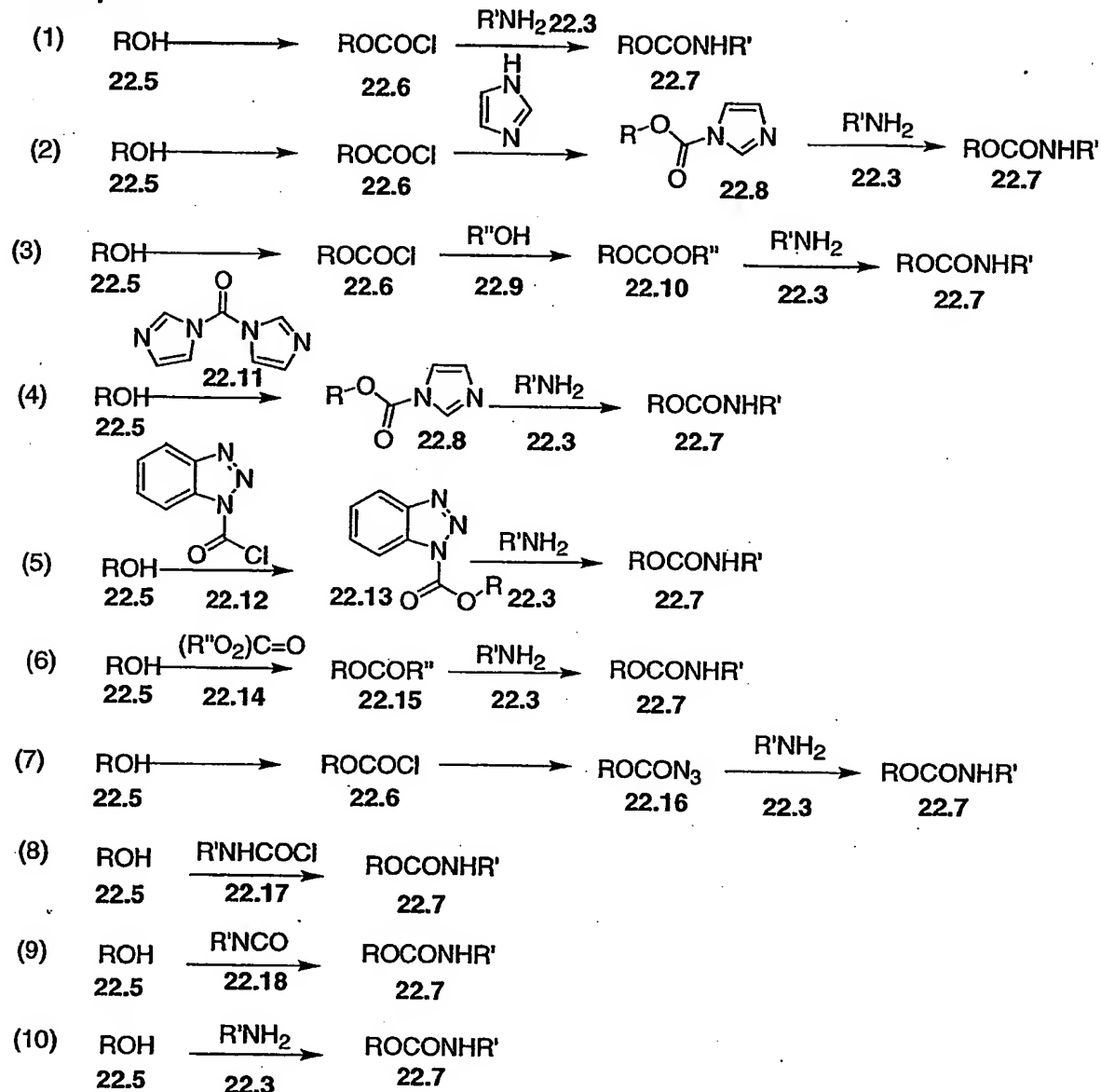


Scheme 22

General reaction



Examples



Preparation of phosphonate intermediates 4 and 5 with phosphonate moieties incorporated into the groups R^2COOH and R^3COOH .

5 The chemical transformations described in Schemes 1-22 illustrate the preparation of compounds 1-3 in which the phosphonate ester moiety is attached to the dimethylphenoxyacetyl (R^3) substructure, (Schemes 1-3), the phenylalanine moiety (Schemes 4-6), and the benzyl moiety (Schemes 7, 8).

The various chemical methods employed herein (Schemes 9-22) for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R^2COOH and R^3COOH , as defined in Charts 2a, 2b, and 2c. The resultant phosphonate-containing analogs $R^{2a}COOH$ and $R^{3a}COOH$ can then, using the procedures described above, be employed in the preparation of the compounds 4 and 5. The procedures required for the introduction of the phosphonate-containing analogs $R^{2a}COOH$ and $R^{3a}COOH$ are the same as those described above (Schemes 4, 5 and 22) for the introduction of the R^2CO and R^3CO moieties.

For example, Schemes 23 - 27 illustrate methods for the preparation of hydroxymethyl-substituted benzoic acids (structure C25, Chart 2b) incorporating phosphonate moieties; Schemes 28-30 illustrate the preparation of tetrahydropyrimidine aminoacid derivatives (structure C27, Scheme 2b) incorporating phosphonate ester moieties, and Schemes 31-33 show the syntheses of benzyl carbamate aminoacid derivatives (structure C4, Chart 2a) incorporating phosphonate ester moieties. The thus-obtained phosphonate ester synthons are then incorporated into the compounds 4 and 5.

Scheme 23 illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid 23.1 is subjected to halogen-methyl exchange to afford the organometallic intermediate 23.2. This compound is reacted with a chlorodialkyl phosphite 23.3 to yield the phenylphosphonate ester 23.4, which upon deprotection affords the carboxylic acid 23.5.

30 For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, 23.6, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Amer. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The

acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane 23.7, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester 23.8. This compound is treated with boron trifluoride at 0° to effect rearrangement to the orthoester 23.9, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether 23.10. Halogen-metal exchange is performed by the reaction of 23.10 with butyllithium, and the lithiated intermediate is then coupled with a chlorodialkyl phosphite 23.3, to produce the phosphonate 23.11. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid 23.12.

Using the above procedures, but employing, in place of the bromo compound 23.6, different bromo compounds 23.1, there are obtained the corresponding products 23.5.

Scheme 24 illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

In this method, a suitably protected dimethyl hydroxybenzoic acid, 24.1, is reacted with a brominating agent, so as to effect benzylic bromination. The product 24.2 is reacted with a sodium dialkyl phosphite, 24.3, as described in J. Med. Chem., 1992, 35, 1371, to effect displacement of the benzylic bromide to afford the phosphonate 24.4. Deprotection of the carboxyl function then yields the carboxylic acid 24.5.

For example, 2,5-dimethyl-3-hydroxybenzoic acid, 24.6, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p17, to afford the ether ester 24.7. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or diisopropylethylamine. The product 24.7 is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product 24.8. This compound is then reacted with a sodium dialkyl phosphite 24.3 in tetrahydrofuran, as described above, to afford the phosphonate 24.9. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid 24.10.

Using the above procedures, but employing, in place of the methyl compound 24.6, different methyl compounds 24.1, there are obtained the corresponding products 24.5.

Scheme 25 illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom.

In this method, a suitably protected hydroxy- or mercapto-substituted hydroxymethyl benzoic acid 25.1 is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl hydroxymethyl phosphonate 25.2, to afford the coupled product 25.3, which upon deprotection affords the carboxylic acid 25.4.

For example, 3,6-dihydroxy-2-methylbenzoic acid, 25.6, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester 25.7, by treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 77, to afford the mono-silyl ether 25.8. This compound is then reacted with a dialkyl hydroxymethylphosphonate 25.2, under the conditions of the Mitsunobu reaction, as described above (Scheme 15) to afford the coupled product 25.9. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic carboxylic acid 25.10.

Using the above procedures, but employing, in place of the phenol 25.6, different phenols or thiophenols 25.1, there are obtained the corresponding products 25.4.

Scheme 26 depicts the preparation of phosphonate esters attached to the

hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains.

In this method, a dialkyl alkenylphosphonate 26.2 is coupled, by means of a palladium catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid 26.1. The product 26.3 can be deprotected to afford the phosphonate 26.4, or subjected to catalytic hydrogenation to afford the saturated compound, which upon deprotection affords the corresponding carboxylic acid 26.5.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid 26.6, prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester 26.7. This

compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate 26.8, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above (Scheme 11) to afford the product 26.9. Deprotection, or hydrogenation/deprotection, of this compound, as described above, then affords respectively
5 the unsaturated and saturated products 26.10 and 26.11.

Using the above procedures, but employing, in place of the bromo compound 26.6, different bromo compounds 26.1, and/or different phosphonates 26.2, there are obtained the corresponding products 26.4 and 26.5.

10 Scheme 27 illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid 27.1 is converted to the corresponding boronic acid 27.2, by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82. The product is subjected to
15 a Suzuki coupling reaction with a dialkyl bromophenyl phosphonate 27.3. The product 27.4 is then deprotected to afford the diaryl phosphonate product 27.5.

For example, the silylated OBO ester 27.6, prepared as described above, (Scheme 23), is converted into the boronic acid 27.7, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate 27.8, prepared as described in J. Chem. Soc. Perkin

20 Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, in the presence of sodium bicarbonate, as described, for example, in Palladium reagents and catalysts J. Tsuji, Wiley 1995, p 218, to afford the diaryl phosphonate 27.9. Deprotection, as described above, then affords the benzoic acid 27.10.

Using the above procedures, but employing, in place of the bromo compound 27.6, different
25 bromo compounds 27.1, and/or different phosphonates 27.3, there are obtained the corresponding carboxylic acid products 27.5.

Scheme 28 illustrates the preparation of analogs of the tetrahydropyrimidine carboxylic acid C27 in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom O, S, or N. In this procedure, an amino acid 28.1, in which R⁴ is as defined in
30 Chart 2b, is converted into the corresponding phenyl carbamate 28.2. The preparation of phenyl carbamates is described in Tet. Lett., 1977, 1936, and in J. Chem. Soc., C, 1967, 2015. The amine substrate is reacted with phenyl chloroformate in the presence of an inorganic or

organic base, such as potassium carbonate or triethylamine, in an organic, aqueous or aqueous organic solvent such as dichloromethane, tetrahydrofuran or water or pyridine. Preferably, the aminoacid 28.1 is reacted with phenyl chloroformate, in water containing lithium hydroxide, lithium chloride and alumina, at a pH of about 9.5, as described in Org. Process Res. Dev., 2000, 4, 264, to afford the phenyl carbamate 28.2. This compound is then reacted with di(3-chloropropyl)amine 28.3, prepared as described in Tet. 1995, 51, 1197, to afford the amide product 28.4. The preparation of amides by reaction of an ester with an amide is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 987. The displacement reaction is effected by treatment of the substrate with the amine, optionally in the presence of a base such as sodium methoxide and the like, to afford the amide product 28.4. Preferably, the carbamate 28.2 and the amine 28.3 are reacted together in tetrahydrofuran, in the presence of sodium hydroxide or lithium hydroxide, to produce the amide product 28.4. The latter compound is then transformed, optionally without isolation, into the chloropropyl-substituted tetrahydropyrimidine product 28.5, by reaction with a strong base such as potassium tert. butoxide in tetrahydrofuran, as described in Org. Process. Res. Dev., 2000, 4, 264. The compound 28.5 is then reacted with a dialkyl hydroxy, mercapto or alkylamino-substituted alkylphosphonate 28.6 to afford the displacement product 28.7. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as sodium hydride, lithium hexamethyldisilazide, potassium carbonate or the like, optionally in the presence of a catalytic amount of potassium iodide, to afford the ether, thioether or amine product 28.7.

Alternatively, the chloropropyl-substituted tetrahydropyrimidine compound 28.5 is transformed into the corresponding propylamine 28.8. The conversion of halo derivatives into amines is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397ff, or Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953 p. 665ff. The chloro compound is reacted with ammonium hydroxide, anhydrous ammonia or hexamethylene tetramine, or with an alkali metal amide such as sodamide to afford the amine product. Preferably, the chloro compound is reacted with potassium phthalimide, and the phthalimido product is then cleaved by treatment with hydrazine, as described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953 p. 679, to afford the amine 28.8. The product is then subjected to a reductive amination reaction with a dialkyl formylalkyl phosphonate 28.9, to yield the phosphonate product 28.10.

For example, as shown in Scheme 28, Example 1, 3-methyl-2-phenoxy-carbonylamino-butyr-
ic acid 28.11, prepared as described in Org. Process Res. Dev., 2000, 4, 264, is reacted with
di(3-chloropropyl)amine, using the conditions described above, to afford 2-[3,3-bis-(3-chloro-
propyl)-ureido]-3-methyl-butyr-ic acid 28.4. The product is then reacted sequentially with
5 sodium hydroxide and then potassium tert. butoxide in tetrahydrofuran, as described in Org.
Process Res. Dev., 2000, 4, 264, so as to afford the cyclized product 2-[3-(3-chloro-propyl)-
2-oxo-tetrahydro-pyrimidin-1-yl]-3-methyl-butyr-ic acid 28.13. The latter compound is then
reacted in dimethylformamide solution at about 70°, with a dialkyl 2-mercaptoethyl
phosphonate 28.14, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, potassium
10 carbonate and a catalytic amount of potassium iodide, to yield the phosphonate ester 28.13.
Using the above procedures, but employing, in place of the valine carbamate 28.11, different
carbamates 28.2, and/or different hetero-substituted alkyl phosphonates 28.6, the
corresponding products 28.7 are obtained.

As a further illustration, Scheme 28, Example 2 depicts the reaction of the chloropropyl
15 tetrahydropyrimidine derivative 28.13 with potassium phthalimide 28.16. Equimolar amounts
of the reactants are combined in dimethylformamide at ca 80°, in the presence of a catalytic
amount of potassium iodide, to afford 2-{3-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-
2-oxo-tetrahydro-pyrimidin-1-yl}-3-methyl-butyr-ic acid 28.17. The product is then reacted
under reductive amination conditions, as described above (Scheme 10) with a dialkyl
20 formylphenyl phosphonate 28.19 (Epsilon) to yield the phosphonate ester product 28.20.
Using the above procedures, but employing, in place of the valine carbamate 28.11, different
carbamates 28.2, and/or different formyl-substituted alkyl phosphonates 28.9, the
corresponding products 28.10 are obtained.

25 Scheme 29 illustrates the preparation of analogs of the tetrahydropyrimidine carboxylic acid
C27 in which the phosphonate moiety is attached by means of an alkylene chain. In this
procedure, an aminoacid 29.1 is subjected to an alkylation reaction with a propanol derivative
29.2 in which Lv is a leaving group such as halo or sulfonyl. The reaction is conducted in
aqueous or aqueous organic solution in the presence of a base such as sodium hydroxide,
30 potassium carbonate and the like, to afford the product 29.3. This compound is then oxidized
to the corresponding aldehyde 29.4. The conversion of alcohols to aldehydes is described, for
example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff.

Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride. The reaction is conducted in an inert aprotic solvent such as pyridine, dichloromethane or toluene. Preferably, the alcohol 29.3 is reacted with an equimolar amount of pyridinium chlorochromate in dichloromethane at ambient temperature, to afford the aldehyde 29.4. This material is then subjected to a reductive amination reaction with a dialkyl aminoalkyl phosphonate 29.5, using the conditions described above (Scheme 10) to produce the phosphonate ester 29.6. The latter compound is then reacted with phosgene, or carbonyldiimidazole or an equivalent reagent, to yield the tetrahydropyrimidine product 29.7. Equimolar amounts of the reagents are combined in an inert polar solvent such as tetrahydrofuran or dimethylformamide at ambient temperature, to effect the cyclization reaction.

For example, 2-(3-hydroxy-propylamino)-3-methyl-butyric acid, the preparation of which is described in Toxicol. Appl. Pharm., 1995, 131, 73, is oxidized, as described above, to afford 3-methyl-2-(3-oxo-propylamino)-butyric acid 29.9. The product is then reacted with a dialkyl aminoethyl phosphonate 29.10, the preparation of which is described in J. Org. Chem., 2000, 65, 676, under reductive amination conditions, to give the product 29.11. This compound is then reacted one molar equivalent of carbonyldiimidazole in dichloromethane, as described in US Patent 5914332, to afford the tetrahydropyrimidine product 29.12.

Using the above procedures, but employing, in place of the valine derivative 29.8, different aminoacid derivatives 29.3, and/or different amino-substituted alkyl phosphonates 29.5, the corresponding products 29.7 are obtained.

Scheme 30 illustrates the preparation of analogs of the tetrahydropyrimidine carboxylic acid C27 in which the phosphonate moiety is attached by means of an alkylene chain. In this procedure, a tetrahydropyrimidine aminoacid derivative, prepared as described in U.S. Patent 5,914,332, is converted into the carboxyl-protected compound 30.2. The protection and deprotection of carboxyl groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. For example, the carboxyl group is protected as a benzyl or substituted benzyl ester, removable by means of hydrogenolysis, or as a tert. butyl ester, removable by treatment with anhydrous acid. The carboxyl-protected derivative 30.2 is then reacted with a dialkyl bromoalkyl phosphonate 30.3, in the presence of a strong base such as sodium hydride, potassium tert. butoxide, lithium

hexamethyldisilazide and the like, in a polar solvent such as dimethylformamide, to afford the alkylation product 30.4. The carboxyl group is then deprotected to yield the carboxylic acid 30.5.

For example, 3-methyl-2-(3-methyl-2-oxo-tetrahydro-pyrimidin-1-yl)-butyric acid 30.6, prepared as described in Org. Process Res. Dev., 200, 4, 264, is converted into the benzyl ester 30.7 by reaction with benzyl alcohol, dicyclohexylcarbodiimide and dimethylaminopyridine in dichloromethane, as described in J. Chem. Soc. Chem. Comm., 1982, 1132. The product is then treated with one molar equivalent of lithium hexamethyldisilazide in dimethylformamide, and the resultant anion is reacted with one molar equivalent of a dialkyl 3-bromopropyl phosphonate 30.8 (Aldrich), to prepare the alkylated product 30.9. The benzyl ester is then converted into the carboxylic acid 30.10, by hydrogenolysis over a palladium catalyst, as described in Org. React., VII, 263, 1953. Using the above procedures, but employing, in place of the valine derivative 30.6, different aminoacid derivatives 30.1, and/or different bromo-substituted alkyl phosphonates 30.3, the corresponding products 30.5 are obtained.

Scheme 31 illustrates the preparation of phosphonate-containing derivatives of the carboxylic acid C4 (Chart 2a) in which the phosphonate group is attached by means of an alkylene chain and a heteroatom O, S or N. In this procedure, a substituted benzyl alcohol 31.1 is reacted with a dialkyl bromoalkyl phosphonate 31.2 to prepare the ether, thioether or amine product 31.3. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium carbonate, optionally in the presence of a catalytic amount of potassium iodide. The benzyl alcohol product 31.3 is then transformed into a formyl derivative 31.4, in which Lv is a leaving group, as described above (Scheme 22). The formate derivative 31.4 is then reacted with a carboxy-protected amino acid 31.5, using the procedures described above for the preparation of carbamates (Scheme 22), to afford the carbamate product 31.6. The carboxy-protecting group is then removed to afford the carboxylic acid 31.7. The carboxyl protecting group present in the aminoacid 31.5 is selected so that the conditions for removal do not cleave the benzyl carbamate moiety in the substrate 31.6.

For example, 3-methylaminobenzyl alcohol 31.8 is reacted in dimethylformamide solution at ca 70° with one molar equivalent of a dialkyl bromoethyl phosphonate 31.9(Aldrich) and

potassium carbonate, to afford the amine 31.10. The product is then with reacted one molar equivalent of carbonyldiimidazole in tetrahydrofuran, to give the imidazolide product 31.11. The compound is then reacted with the tert. butyl ester of valine 31.12, in pyridine at ambient temperature, to afford the carbamate product 31.13. The tert. butyl ester is then removed by
5 treatment of the ester 31.13 with trifluoroacetic acid at 0°, as described in J. Am. Chem. Soc., 99, 2353, 1977, to afford the carboxylic acid 31.14.

Using the above procedures, but employing, in place of the benzyl alcohol derivative 31.8, different benzyl alcohols 31.1, and/or different bromo-substituted alkyl phosphonates 31.2, the corresponding products 31.7 are obtained.

10 Scheme 32 illustrates the preparation of phosphonate-containing derivatives of the carboxylic acid C4 (Chart 2a) in which the phosphonate group is attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted benzyl alcohol 32.1 is coupled, in the presence of a palladium catalyst, with a dialkyl alkenylphosphonate 32.2. The
15 coupling reaction between aryl bromides and olefins is described above (Scheme 11). The coupled product 32.3 is then converted into the carbamate derivative 32.5, by means of the series of reactions illustrated above (Scheme 31) for the conversion of the benzyl alcohol 31.3 into the carbamate derivative 31.7. Alternatively, the unsaturated compound 32.3 is reduced,

20 Larock, VCH, 1989, p.8, to produce the saturated analog 32.4. This material as then transformed, as described above, into the carbamate derivative 32.6.

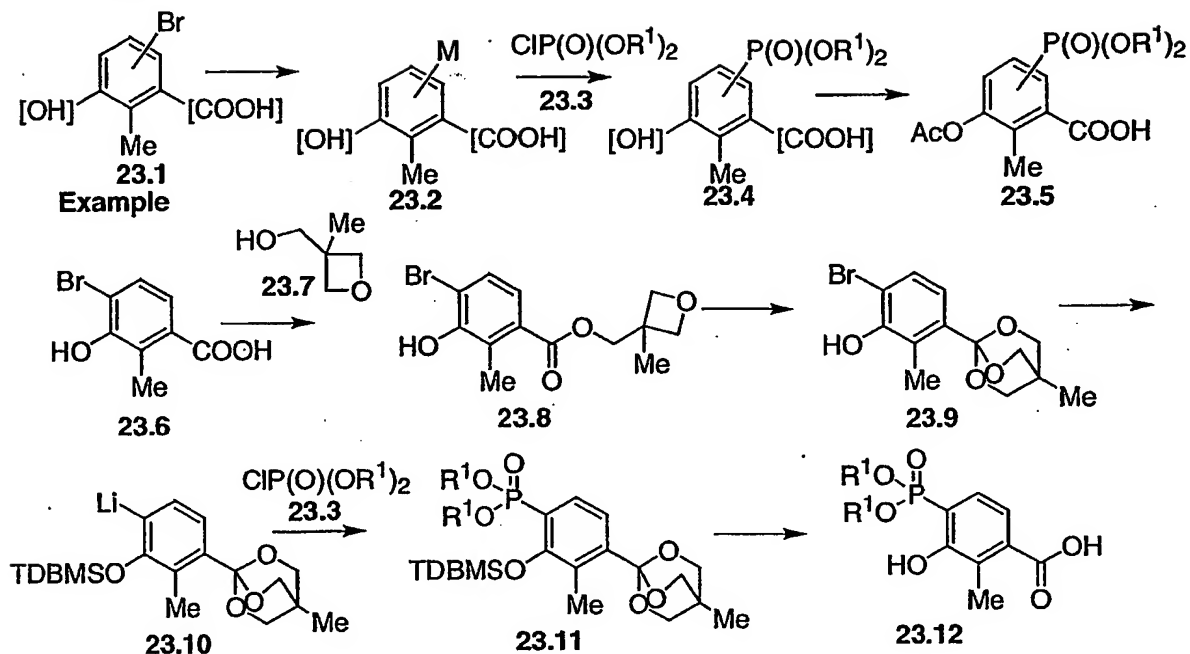
For example, 4-bromobenzyl alcohol 32.7 is coupled, in the presence of diethyl vinylphosphonate, prepared as described in Synthesis, 1983, 556, in the presence of ca. 3 mol % of palladium(II) acetate, triethylamine and tri(o-tolyl)phosphine in acetonitrile at ca. 100°
25 in a sealed tube, as described in Synthesis, 1983, 556, to produce the coupled product 32.9. The product is then converted, as described above, into the unsaturated and saturated carbamate derivatives 32.10 and 32.11.

Using the above procedures, but employing, in place of 4-bromobenzyl alcohol 32.7, different benzyl alcohols 32.1, and/or different dialkyl alkenyl phosphonates 32.2, the corresponding
30 products 32.5 and 32.6 are obtained.

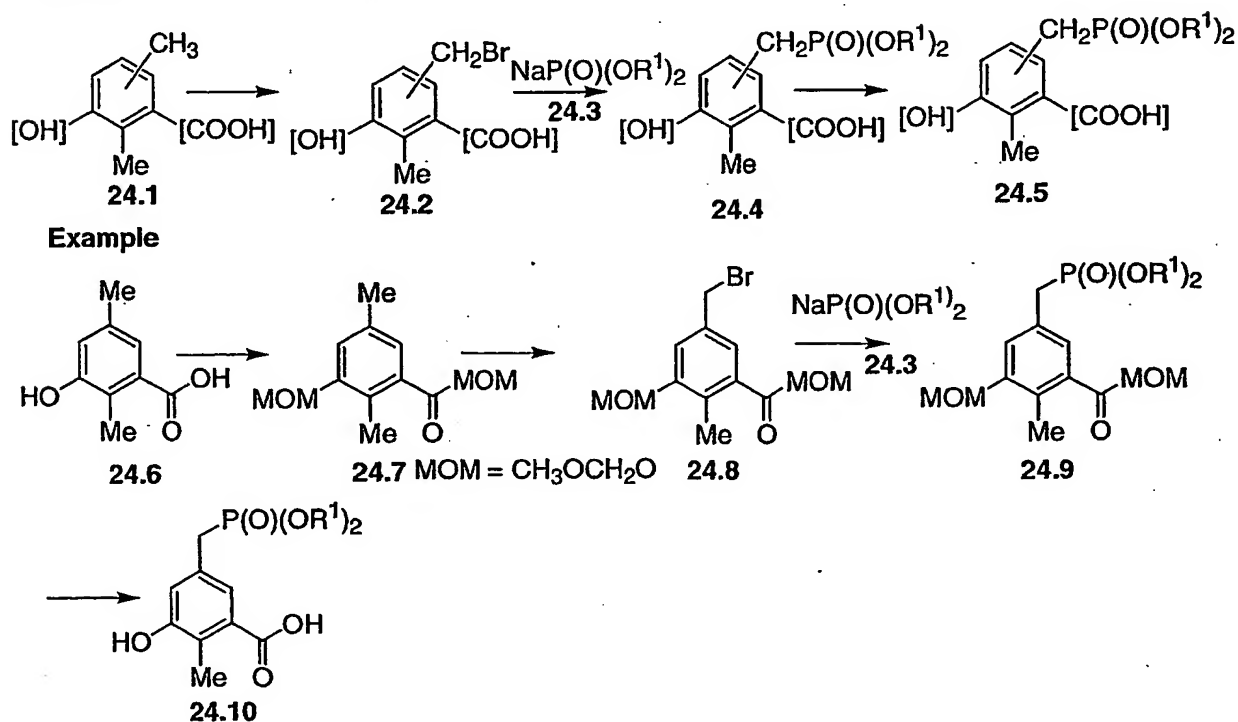
Scheme 33 illustrates the preparation of phosphonate-containing derivatives of the carboxylic acid C4 (Chart 2a) in which the phosphonate group is attached by means of a phenyl ring. In this procedure, a benzaldehyde boronic acid 33.1 is coupled, using the procedures described above (Scheme 27) with a dialkyl bromophenylphosphonate 33.2, to afford the biphenyl derivative 33.3. The aldehyde group is then reduced to give the corresponding benzyl alcohol 33.4. The reduction of aldehydes to afford alcohols is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968. The conversion can be effected by the use of reducing agents such as sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride, diborane and the like. Preferably, the aldehyde 33.3 is reduced to the carbinol 33.4 by reaction with sodium borohydride in ethanol at ambient temperature. The resulting benzyl alcohol is then transformed, using the procedures described above, (Scheme 31) into the carbamate derivative 33.5.

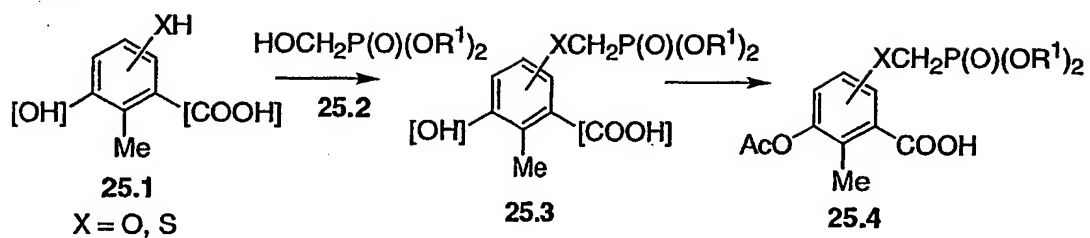
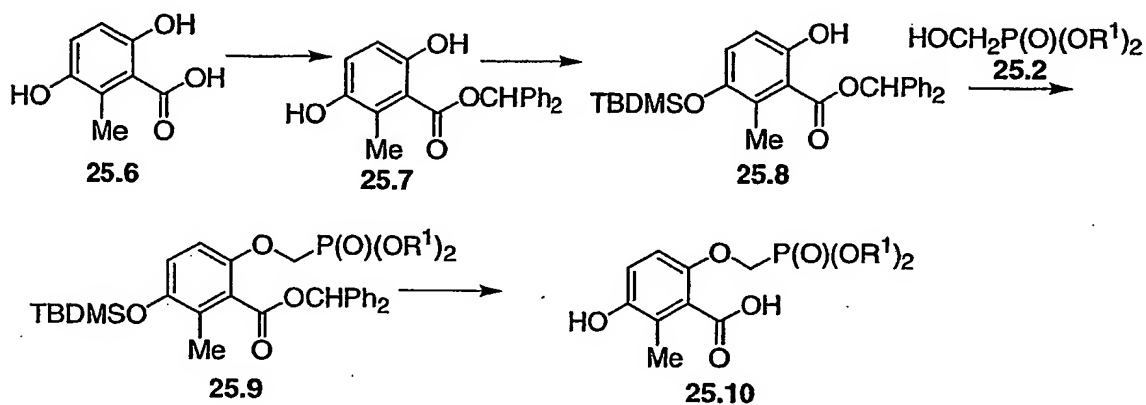
For example, 3-formylphenylboronic acid 33.6 (Fluka) is coupled with a dialkyl 4-bromophenylphosphonate 33.7, prepared as described in J. Organomet. Chem., 1999, 581, 62, in the presence of tetrakis(triphenylphosphine)palladium and sodium bicarbonate, as described in Palladium Reagents and Catalysts, by J. Tsuji, Wiley 1995, p. 218, to yield the diphenyl compound 33.8. The aldehyde group is reduced to afford the carbinol 33.9, and the latter compound is then transformed, as described above, into the carbamate derivative 33.10. Using the above procedures, but employing, in place of the benzaldehyde 33.6, different benzaldehydes 33.1, and/or different dialkyl bromophenyl phosphonates 33.2, the corresponding products 33.4 are obtained.

Scheme 23
Method



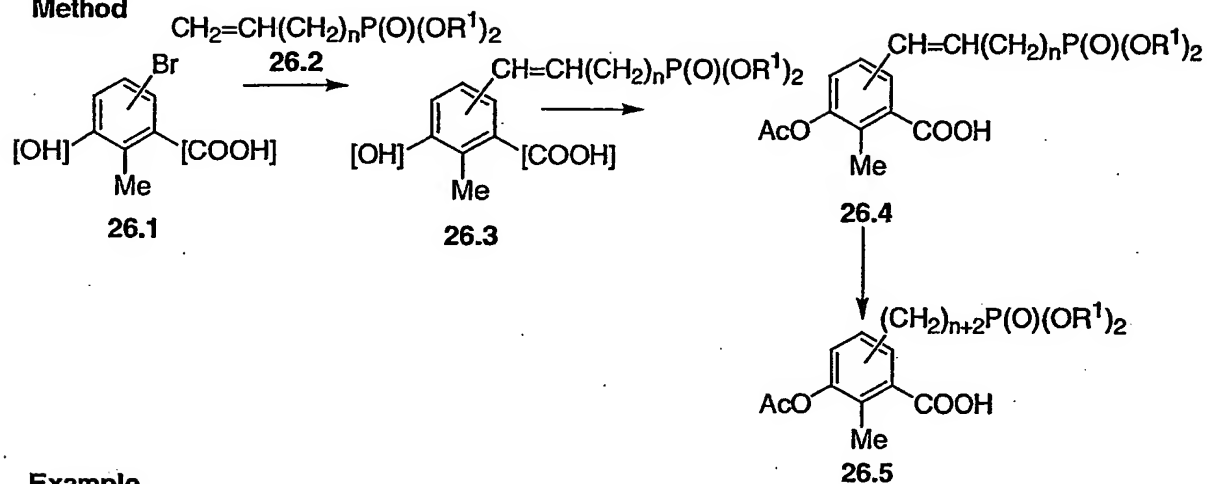
Scheme 24
Method



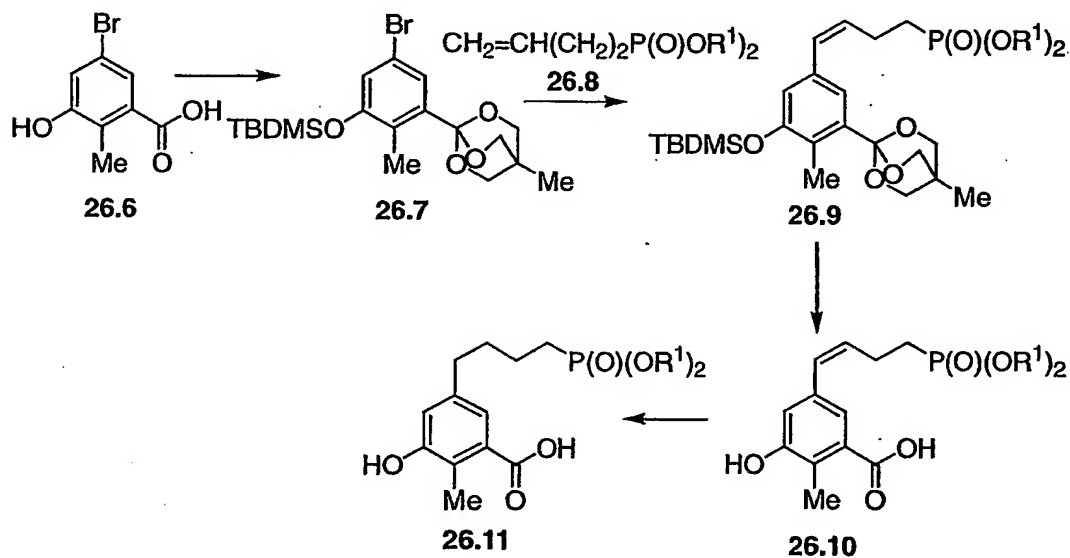
Scheme 25**Method****Example**

Scheme 26

Method

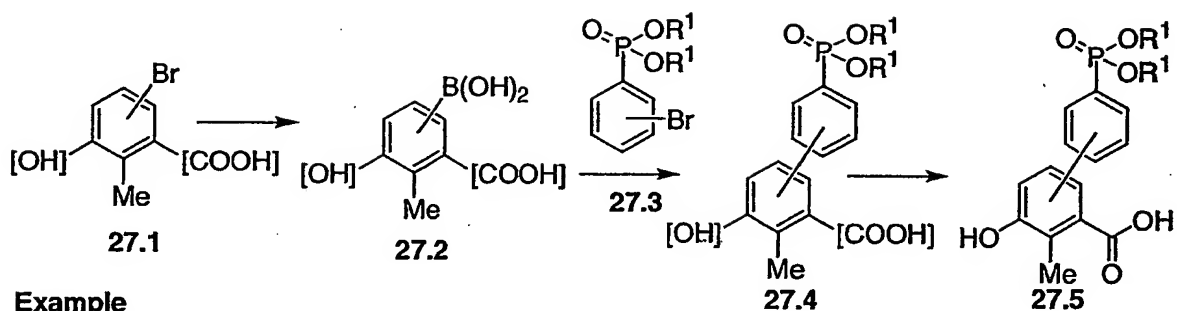


Example

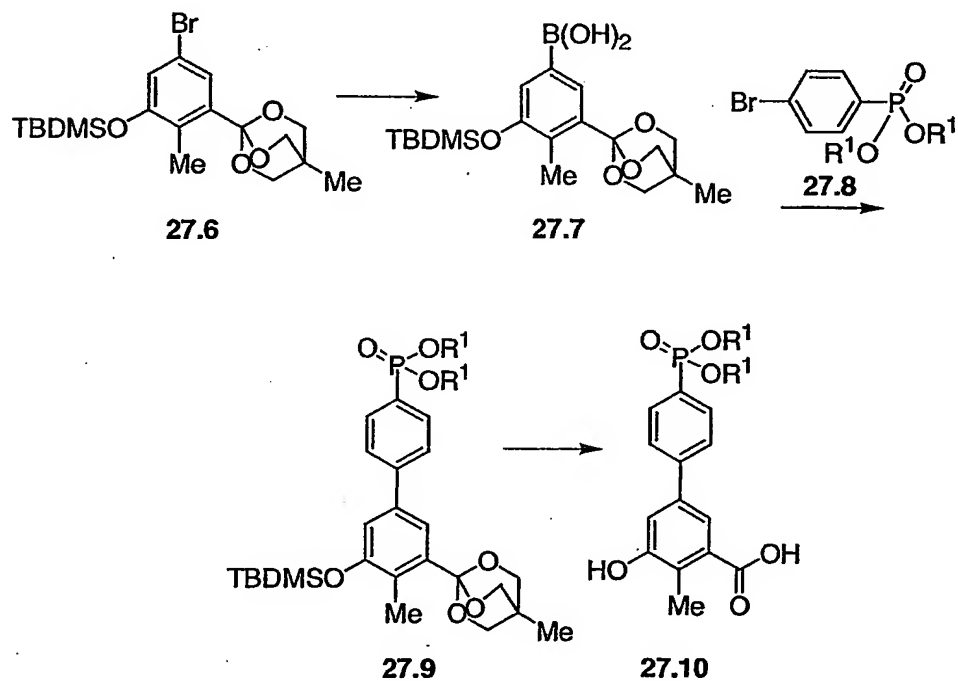


Scheme 27

Method

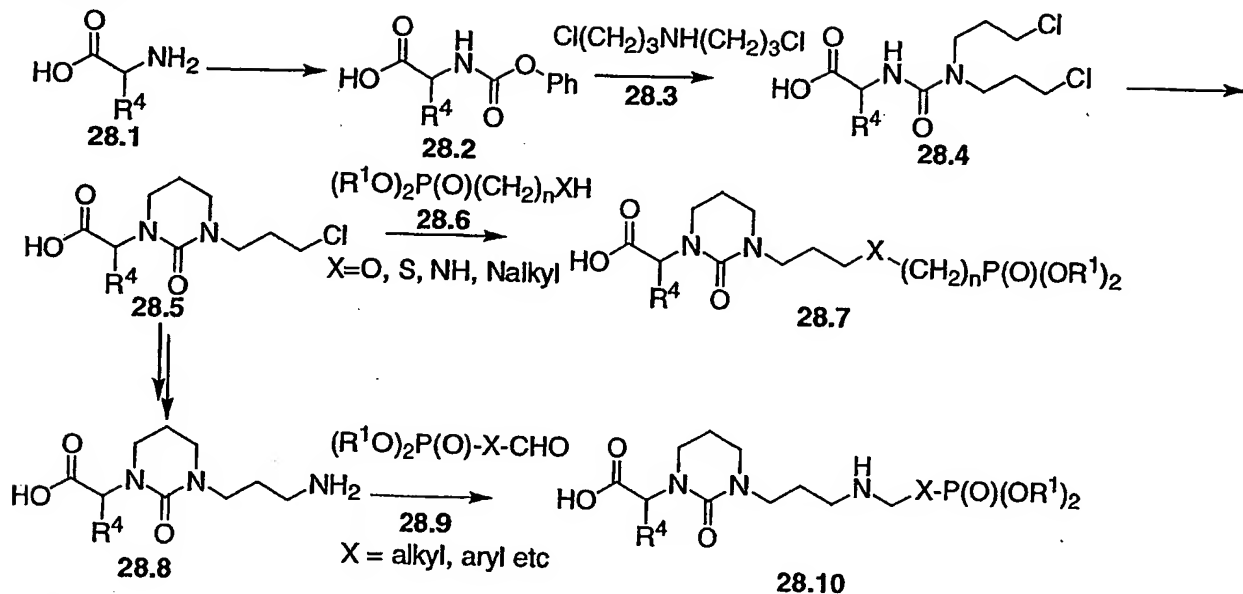


Example

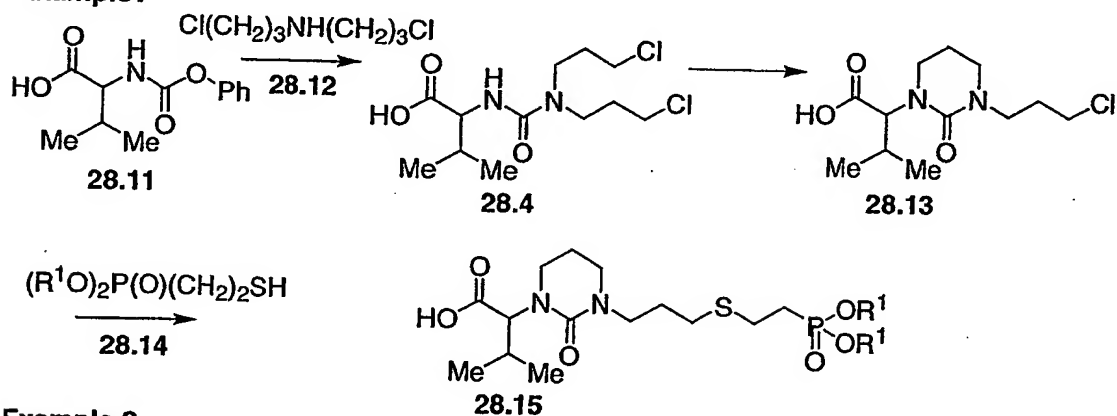


Scheme 28

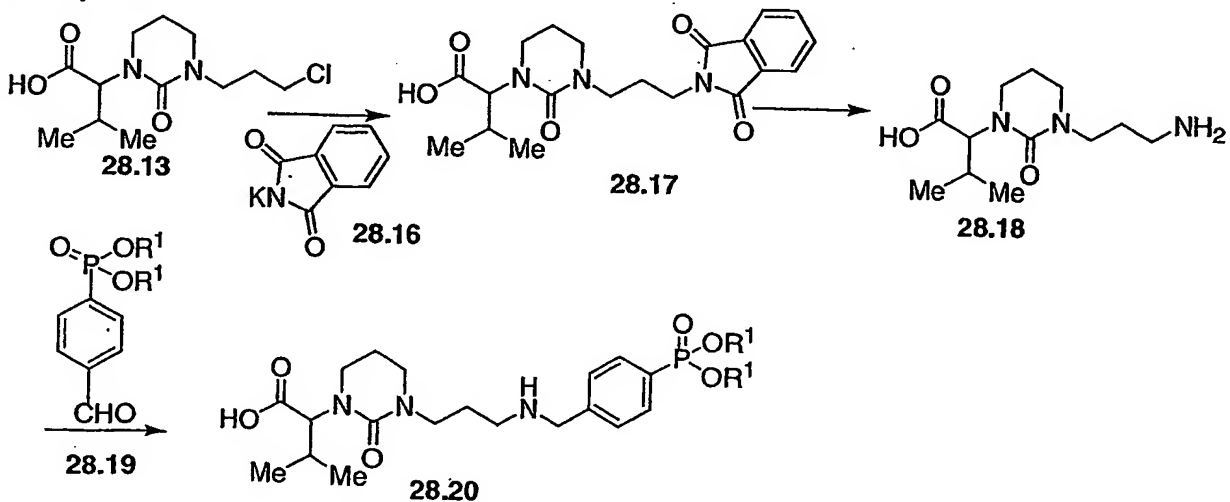
Method



Example1

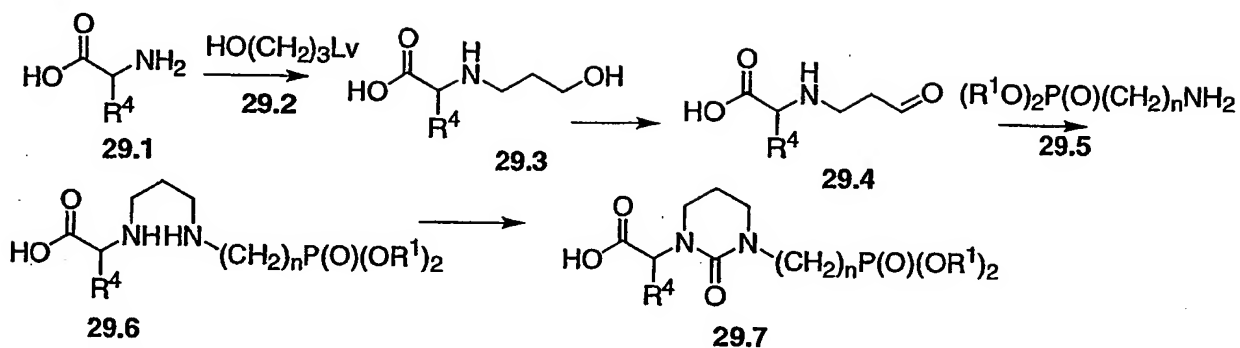


Example 2

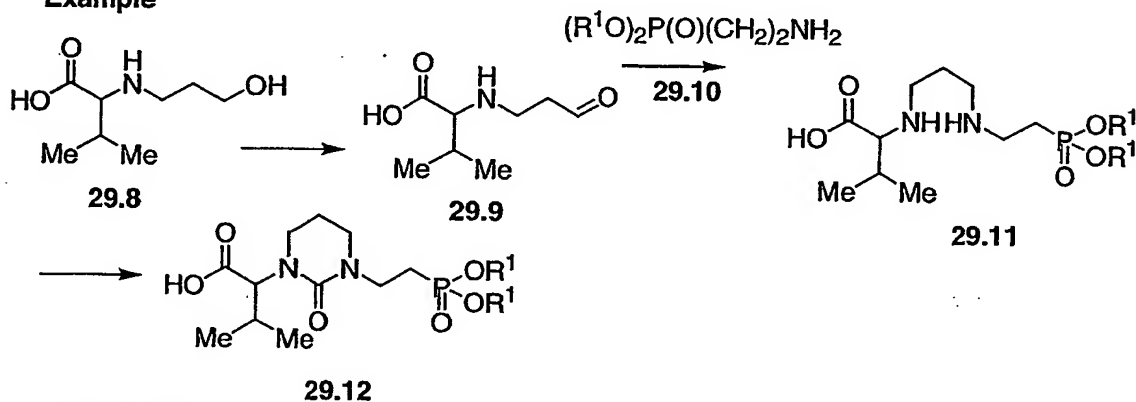


Scheme 29

Method

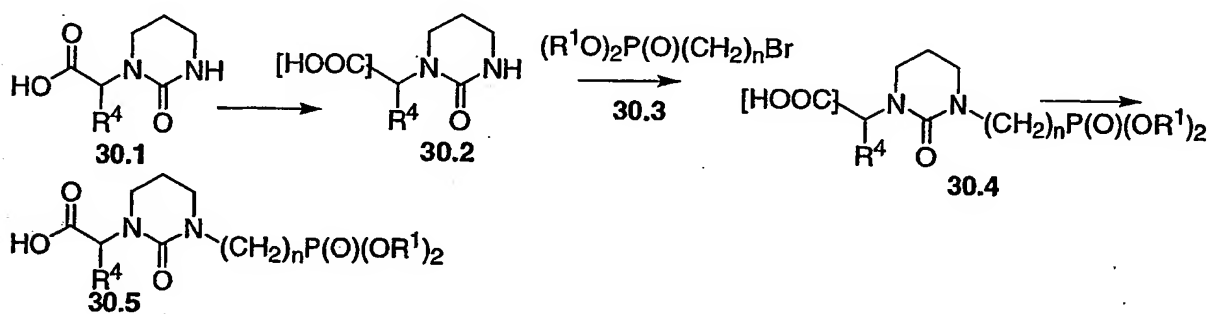


Example

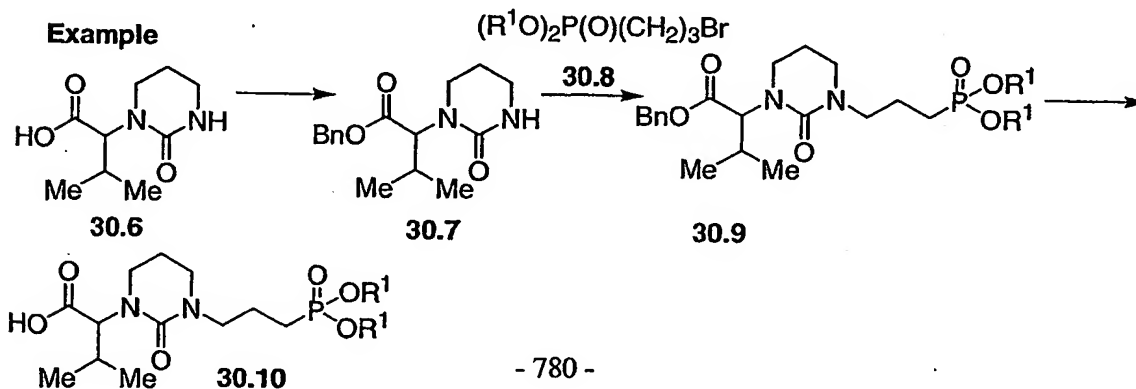


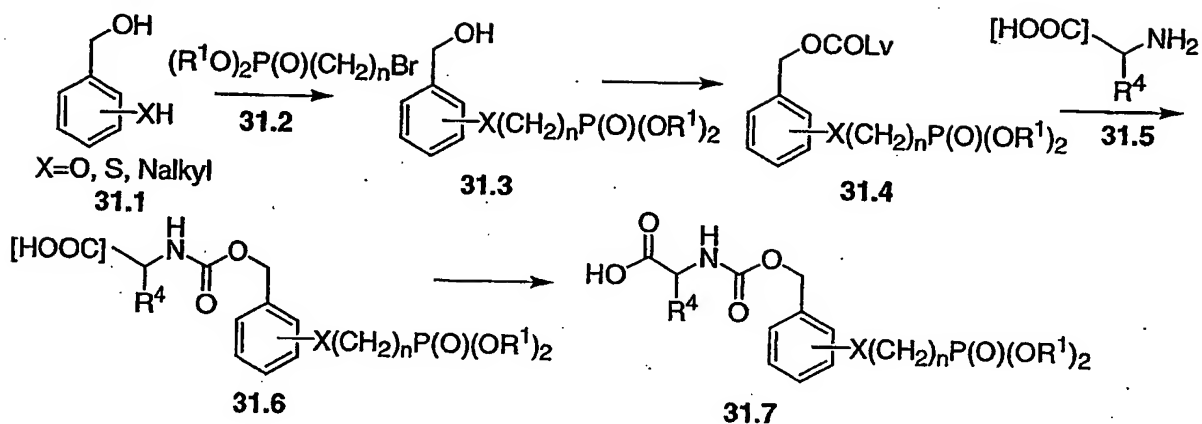
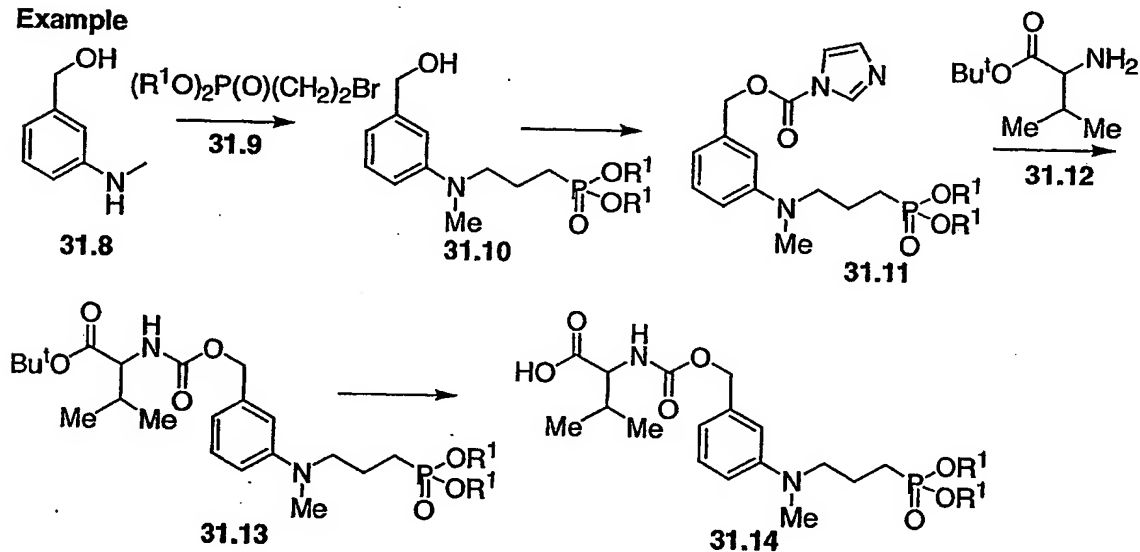
Scheme 30

Method



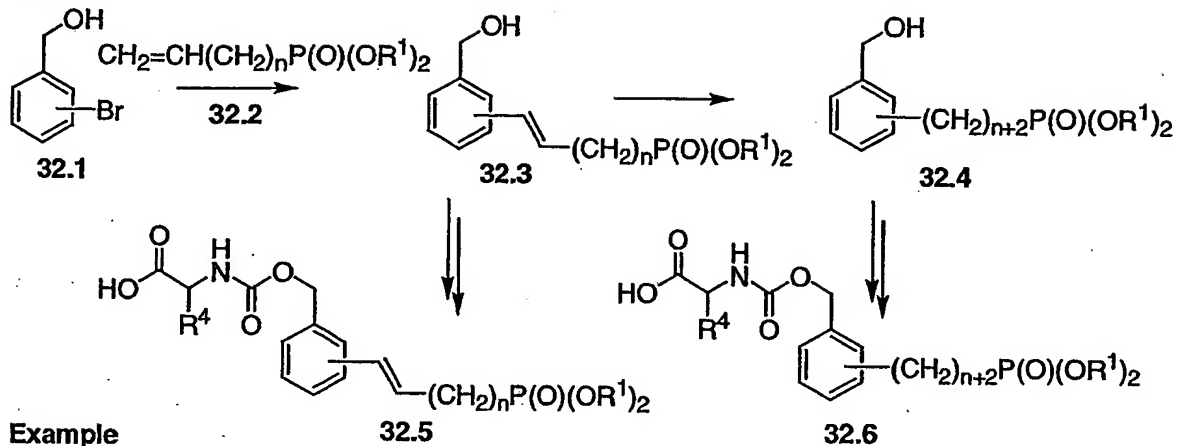
Example



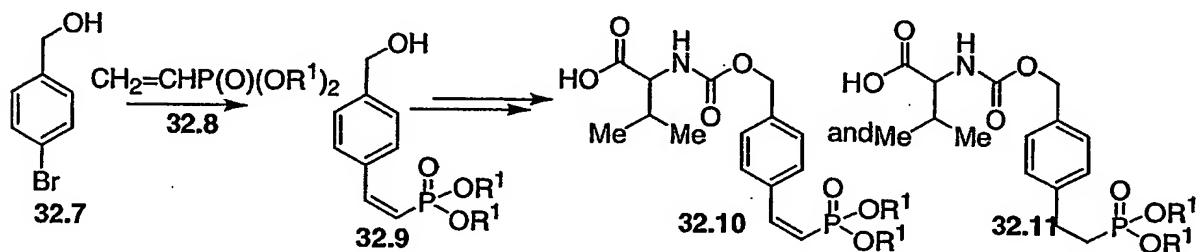
Scheme 31**Method****Example**

Scheme 32

Method

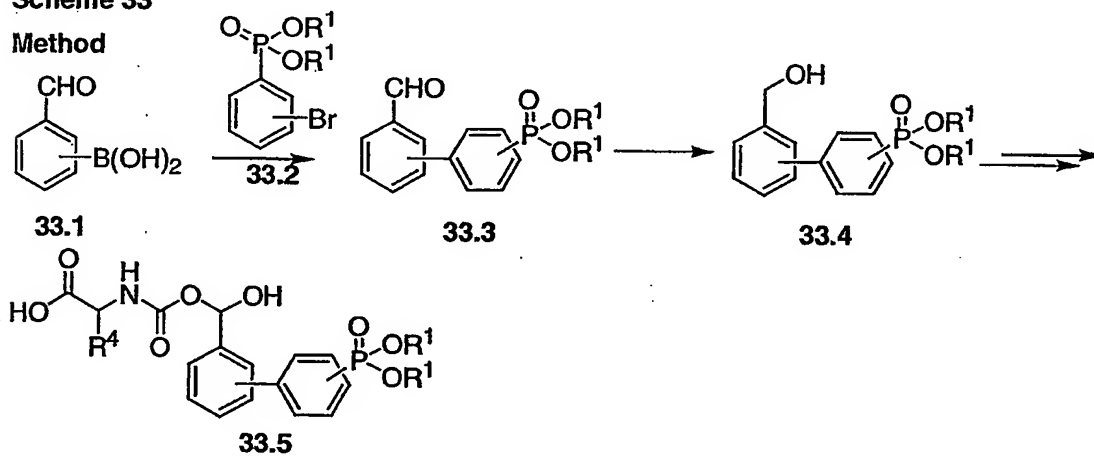


Example

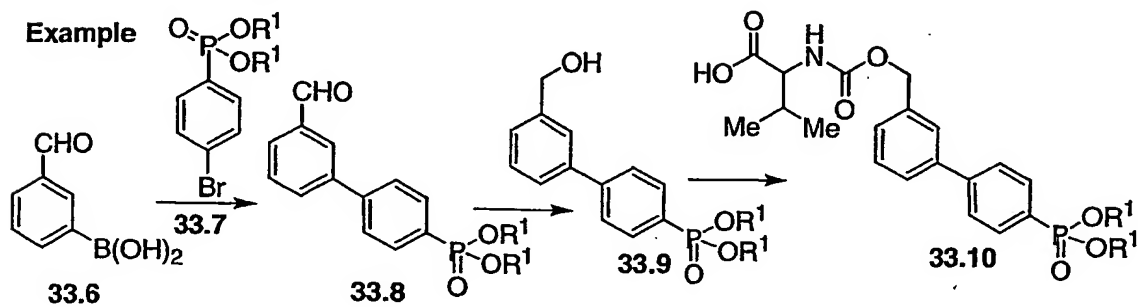


Scheme 33

Method



Example



General applicability of methods for introduction of phosphonate substituents.

The methods described herein for the preparation of phosphonate ester intermediate compounds are, with appropriate modifications, generally applicable to different substrates, such as the carboxylic acids depicted in Charts 2a, 2b and 2c. Thus, the methods described above for the introduction of phosphonate groups into the dimethylphenoxyacetic acid moiety (Schemes 9-14), can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the phenylalanine synthon for the preparation of the phosphonate esters 3. Similarly, the methods described above for the introduction of phosphonate groups into the phenylalanine moiety (Schemes 15-17), the hydroxy methyl substituted benzoic acids (Schemes 23- 27), the tetrahydropyrimidine analogs (Schemes 28-30), and the benzyl carbamates (Schemes 31- 33) can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the dimethylphenoxyacetic acid component.

Atazanavir-like phosphonate protease inhibitors (ATLPPD)

Preparation of the intermediate phosphonate esters.

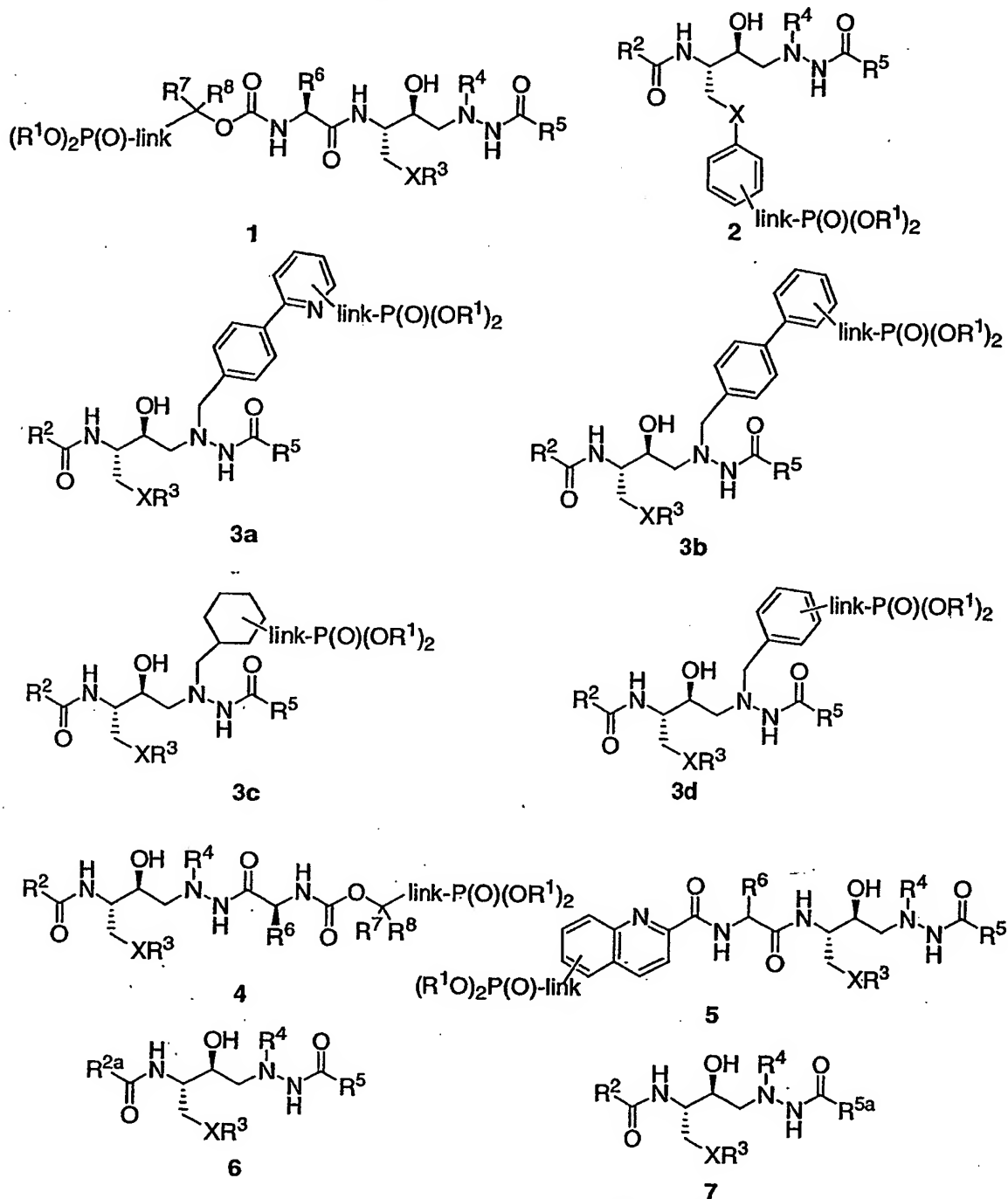
The structures of the intermediate phosphonate esters 1 to 7, and the structures for the component groups X, R¹, R⁷ and R⁸ of this invention are shown in Chart 1. The structures of the R²COOH and R⁵COOH components are shown in Charts 2a, 2b and 2c, and the structures of the R³XCH₂ components are shown in Chart 3. The structures of the R⁴ components are shown in Chart 4. Specific stereoisomers of some of the structures are shown in Charts 1-4; however, all stereoisomers are utilized in the syntheses of the compounds 1 to 7. Subsequent chemical modifications to the compounds 1 to 7, as described herein, permit the synthesis of the final compounds of this invention.

The intermediate compounds 1 to 7 incorporate a phosphonate moiety (R¹O)₂P(O) connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts 5 and 6 illustrate examples of the linking groups present in the structures 1 - 7. The term "etc" in Charts 3, 5 and 6, refers to the scaffold atazanavir.

Schemes 1 - 56 illustrate the syntheses of the intermediate phosphonate compounds of this invention, 1- 5, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters 6 and 7, in which the phosphonate moiety is incorporated into the groups R^2COOH and R^5COOH , are also described below.

5

Chart 1. Structures of the phosphonate esters 1 - 7.



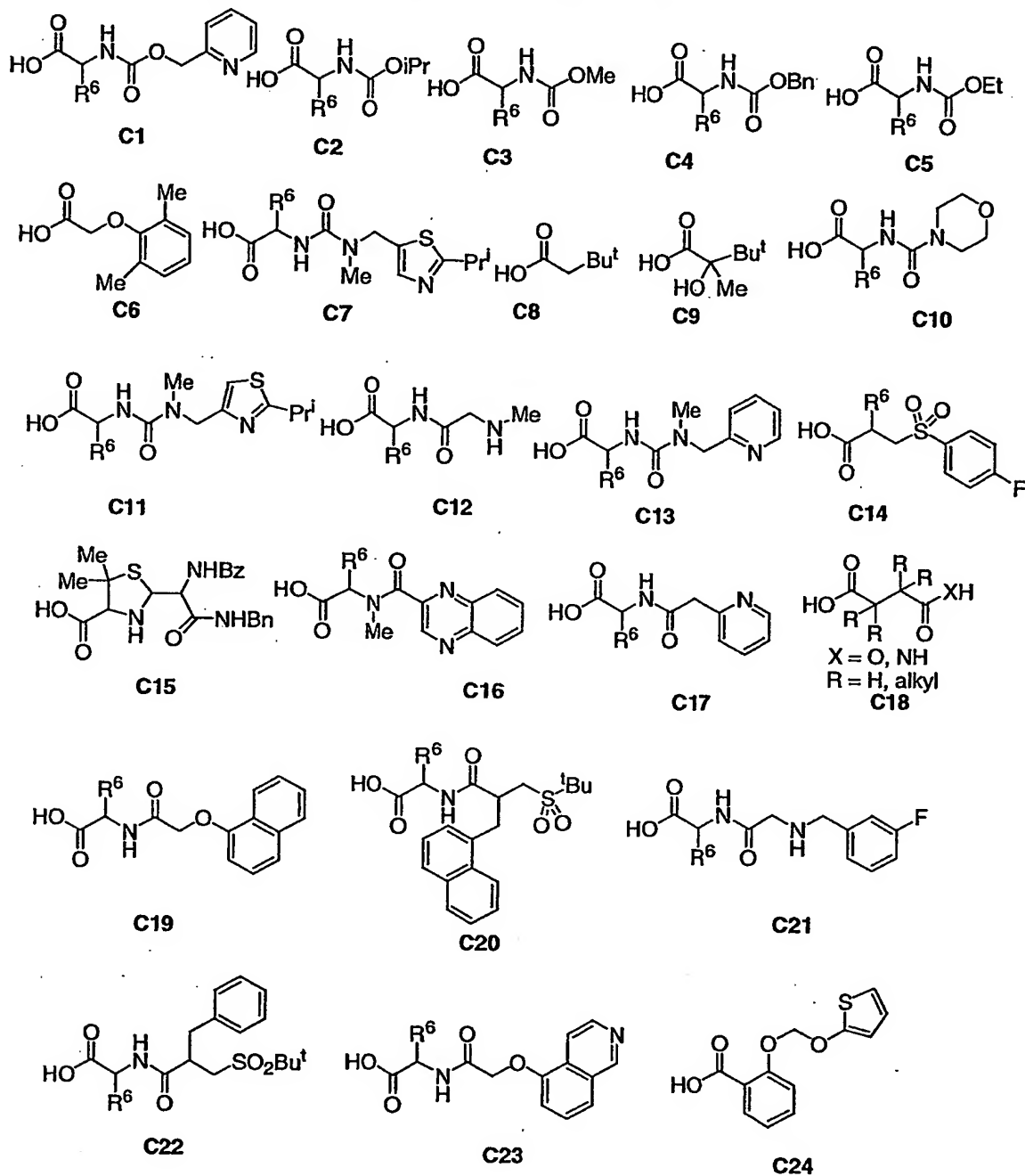
R^{2a} = phosphonate-containing R^2

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

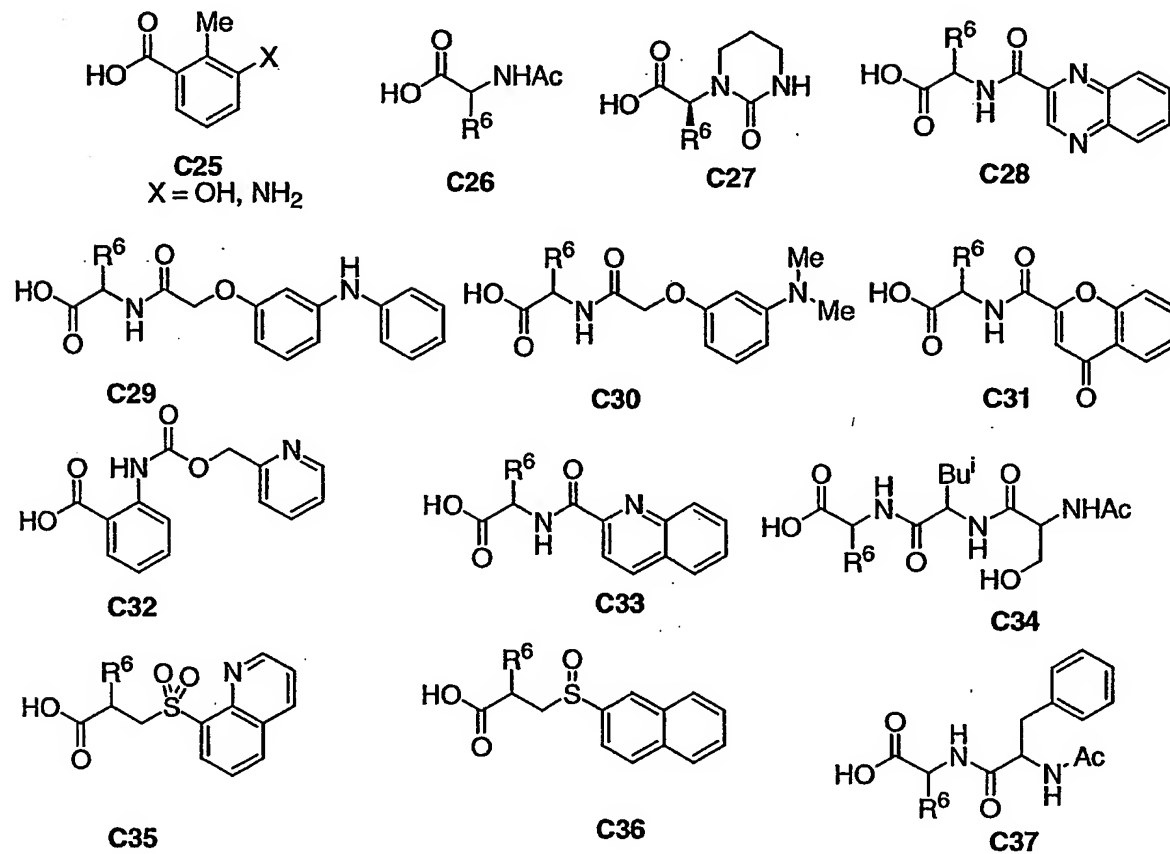
R^7, R^8 = H, alkyl

X = direct bond; sulfur.

R^{5a} = phosphonate-containing R^5

Chart 2a Structures of the R²COOH and R⁵COOH components

$R^6 = alkyl, CH_2SO_2CH_3, C(CH_3)_2SO_2CH_3, CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl,$
 $CH_2NHAc, CH_2NHCOCF_3$

Chart 2b Structures of the R²COOH and R⁵COOH components

R⁶ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, NHAc, NHCOCF₃

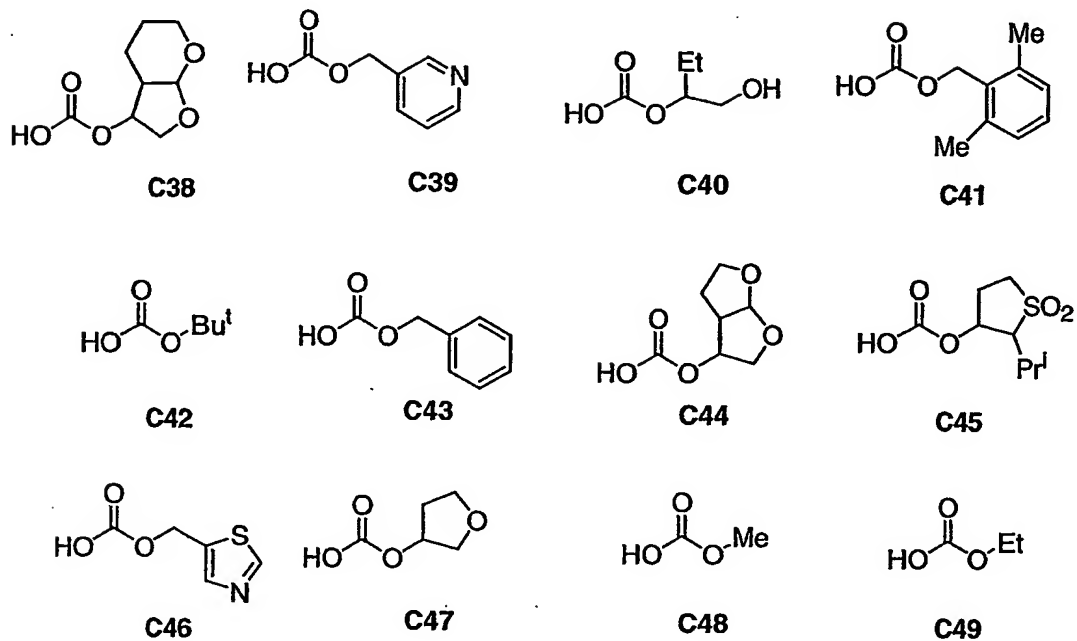
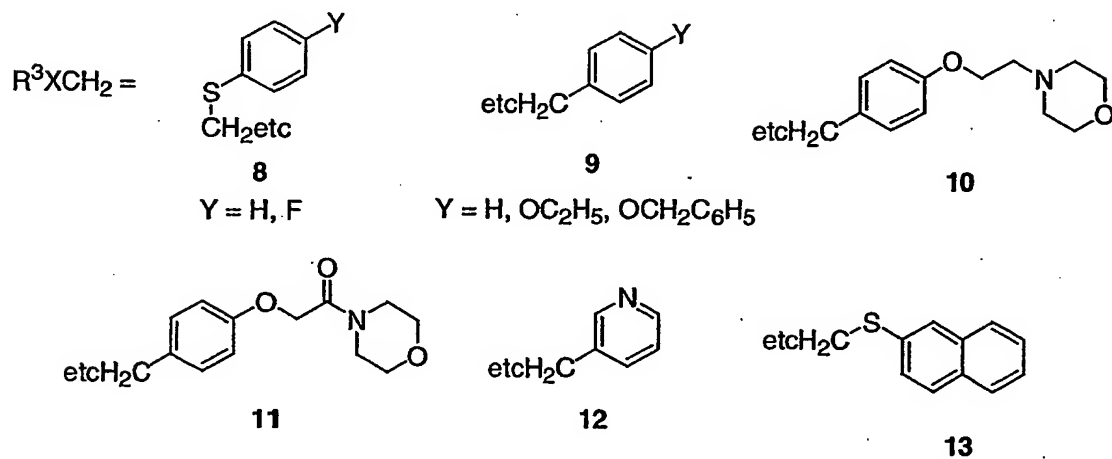
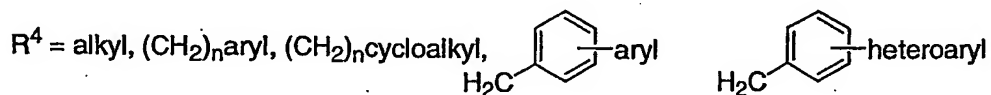
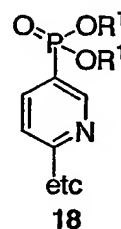
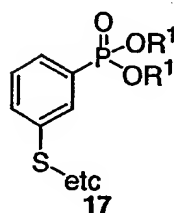
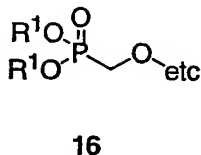
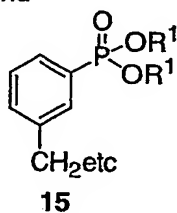
Chart 2c Structures of the R²COOH and R⁵COOH componentsChart 3 Structures of the R³XCH₂ groups.Chart 4 Structures of the R⁴ groups

Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.

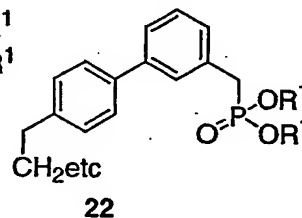
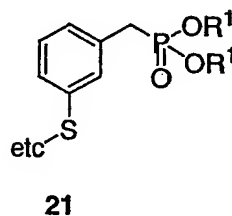
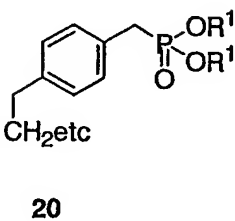
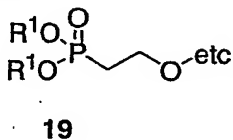
link

examples

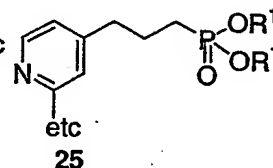
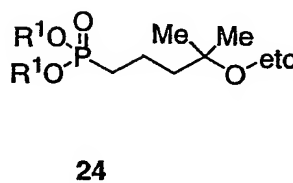
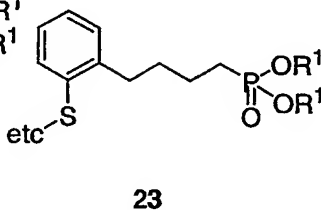
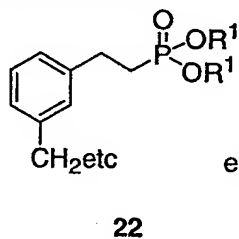
direct bond



single carbon



multiple carbon



hetero atoms

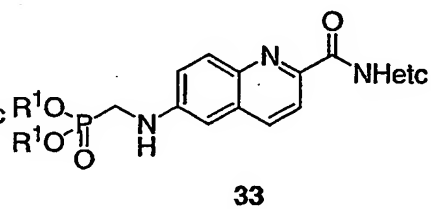
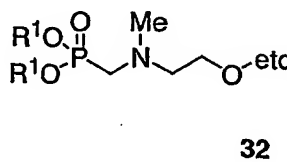
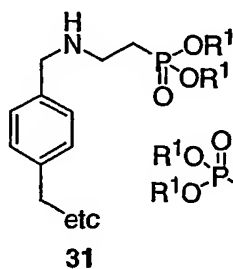
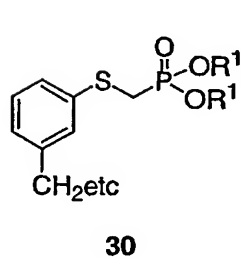
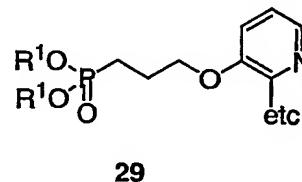
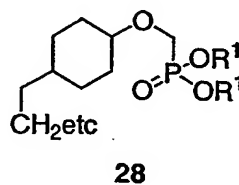
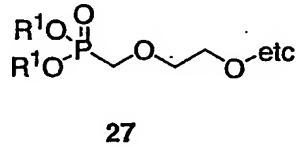
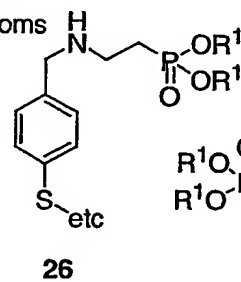
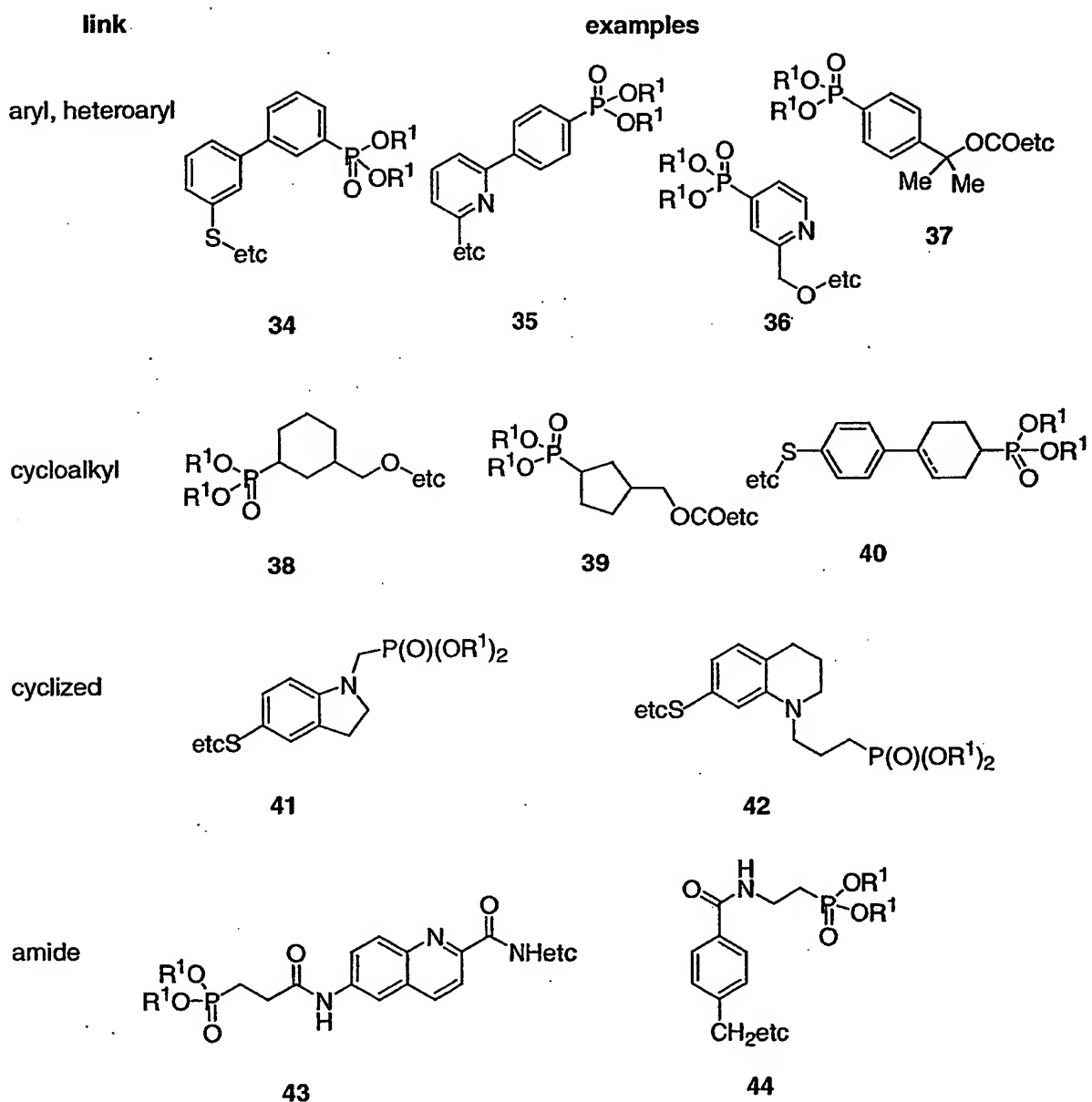


Chart 6 Examples of the linking group between the scaffold and the phosphonate moiety.



Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain
5 reactive substituents from unwanted reactions by protection before the sequence described,
and to deprotect the substituents afterwards, according to the knowledge of one skilled in the
art. Protection and deprotection of functional groups are described, for example, in *Protective
Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990.
Reactive substituents which may be protected are shown in the accompanying schemes as, for
10 example, [OH], [SH].

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

Schemes 1 and 2 illustrate the preparation of the phosphonate esters 1 in which X is a direct
15 bond. As shown in Scheme 1, the oxirane 1.1 is reacted with the BOC-protected hydrazine
derivative 1.2 to afford the aminoalcohol 1.3. The preparation of the oxiranes 1.1, in which Y
is as defined in Scheme 1, is described below, (Scheme 3). The preparation of the hydrazine
derivatives $R^4NHNHBOC$ is described below, (Scheme 4). The reaction between the oxirane
1.1 and the hydrazine 1.2 is conducted in a polar organic solvent such as dimethylformamide,
20 acetonitrile or, preferably, a lower alkanol. For example, equimolar amounts of the reactants
are combined in isopropanol and heated to ca. 80° for about 16 hours, as described in WO
9740029, to afford the aminoalcohol 1.3. The cbz protecting group is then removed from the
product to yield the free amine 1.4. The removal of carbobenzyloxy substituents to afford the
corresponding amines is described in *Protective Groups in Organic Synthesis*, by T.W. Greene
25 and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion can be effected by the
use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a
palladium catalyst. Alternatively, the cbz group can be removed by treatment of the substrate
with triethylsilane, triethylamine and a catalytic amount of palladium (II) chloride, as described
in *Chem. Ber.*, 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient
30 temperature, as described in *J. Chem. Soc., Perkin Trans. I*, 1277, 1988. The cbz group can
also be removed by treatment with a Lewis acid such as boron tribromide, as described in *J.
Org. Chem.*, 39, 1247, 1974, or aluminum chloride, as described in *Tet. Lett.*, 2793, 1979.

Preferably, the protected amine 1.3 is converted into the free amine 1.4 by means of hydrogenation over 10% palladium on carbon catalyst in ethanol, as described in US Patent 5196438.

5 The amine product 1.4 is then reacted with a carboxylic acid 1.5 to afford the amide 1.6. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the
10 presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, imidazolide and the like, and then reacted with the amine, in the presence of
15 an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane. Preferably, equimolar amounts of the amine and the carboxylic acid are reacted in tetrahydrofuran at ca. -10° , in the presence
20 of dicyclohexylcarbodiimide, as described in U.S. Patent 5,196,438, to afford the aminoamide 1.6. The aminoamide is then reacted with a reagent A-CR⁷R⁸OCOX (1.7), in which the substituent A is the group (R¹O)₂P(O)-link, or a precursor group thereto, such as [OH], [SH], [NH], Br, as described below, and in which the substituent X is a leaving group, to yield the carbamate 1.8. The reagent A-CR⁷R⁸OCOX is derived from the corresponding alcohol A-
25 CR⁷R⁸OH, using methods described below, (Scheme 20). The preparation of the reactants A-CR⁷R⁸OCOX is described in Schemes 21 - 26. The preparation of carbamates by means of reactions between alcohols and amines is described in Scheme 20.

The BOC-protected amine present in the carbamate product 1.8 is then deprotected to produce the free amine 1.9. The removal of BOC protecting groups is described, for example,
30 in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid or formic acid, or

by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC group is removed by treatment of the substrate **1.8** with hydrogen chloride in tetrahydrofuran, for example as described in *Org. Process Res. Dev.*, 2002, 6, 323. The resulting amine **1.9** is then coupled with a carboxylic acid or an activated derivative thereof **1.10**, to afford the amide

5 **1.11**, using the conditions described above for the preparation of the amide **1.6**.

For example, the amine **1.9** is reacted with the carboxylic acid **1.10**, $X = OH$, in the presence of a water-soluble carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydroxybenzotriazole and triethylamine, as described in *J. Med. Chem.*, 41, 1988, 3387, to yield the amide **1.11**.

10 The procedures illustrated in Scheme 1 depict the preparation of the compounds **1.11** in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as $[OH]$, $[SH]$, Br, as described below. Scheme 2 illustrates the conversion of compounds **1.11** in which A is a precursor to the group $\text{link-P(O)(OR}^1)_2$ into the compounds **1**. Procedures for the conversion of the substituent A into the group $\text{link-P(O)(OR}^1)_2$ are illustrated below,

15 (Schemes 21 - 56). In the procedures illustrated above, (Scheme 1) and in the procedures illustrated below (Schemes 3 - 19) for the preparation of the phosphonate esters **1 - 7**, compounds in which the group A is a precursor to the group $\text{link-P(O)(OR}^1)_2$ may be converted into compounds in which A is $\text{link-P(O)(OR}^1)_2$ at any appropriate stage in the reaction sequence, or, as shown in Scheme 2, at the end of the sequence. The selection of an

20 appropriate stage to effect the conversion of the group A into the group $\text{link-P(O)(OR}^1)_2$ is made after consideration of the nature of the reactions involved in the conversion, and the stability of the various components of the substrate to those reaction conditions.

Scheme 3 illustrates the preparation of the epoxides **1.1** used above in Scheme 1. The

25 preparation of the epoxide **1.1** in which R^7 is H is described in *J. Org. Chem.*, 1994, 59, 3656. Analogs in which R^7 is one of the substituents defined in Chart 3 are prepared as shown in Scheme 3. A substituted phenylalanine **3.1** is first converted into the benzyloxycarbonyl (cbz) derivative **3.2**. The preparation of benzyloxycarbonyl amines is described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990,

30 p. 335. The aminoacid **3.1** is reacted with benzyl chloroformate or dibenzyl carbonate in the presence of a suitable base such as sodium carbonate or triethylamine, to afford the protected amine product **3.2**. The conversion of the carboxylic acid **3.2** into the epoxide **1.1**, for

example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, and in J. Org. Chem., 1994, 59, 3656 is then effected. The carboxylic acid is first converted into an activated derivative such as the acid chloride 3.3, in which X is Cl, for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone 3.4. The reaction is performed by the addition of a solution of the activated carboxylic acid derivative to an ethereal solution of three or more molar equivalents of diazomethane at 0°. The diazoketone 3.4 is converted into the chloroketone 3.5 by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether, as described in J. Org. Chem., 1994, 59, 3656. The latter compound is then reduced, for example by the use of an equimolar amount of sodium borohydride in an ethereal solvent such as tetrahydrofuran at 0°, to produce a mixture of chlorohydrins from which the minor diastereomer 3.6 is separated by chromatography. The chlorohydrin 3.6 is then converted into the epoxide 1.1 by treatment with a base such as an alkali metal hydroxide in an alcoholic solvent, for example as described in J. Med. Chem., 1997, 40, 3979. Preferably, the compound 3.6 is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide 1.1. The preparations of analogs of the oxirane 1.1 in which the amino group is protected respectively as the tert-butoxycarbonyl and trifluoroacetyl derivatives are described respectively in J. Med. Chem., 1994, 37, 1758 and J. Med. Chem., 1996, 39, 3203.

Scheme 4 depicts the preparation of the hydrazine derivatives 1.2, in which R⁴ is CH₂-aryl, CH₂-alkyl, CH₂-cycloalkyl as shown in Chart 4. The general procedure for the preparation of BOC-protected hydrazine derivatives from the corresponding aldehyde RCHO (4.1) is shown in Scheme 4. The aldehyde is reacted with tert. butyl carbazate 4.2, in a solvent such as an alkanol, a hydrocarbon such as toluene, or a polar organic solvent such as dimethylformamide, to afford the substituted hydrazone 4.3. Preferably, equimolar amounts of the reactants are heated in a mixture of toluene and isopropanol, as described in Org. Process Res. Dev., 2002, 6, 323, to prepare the hydrazone 4.3. The product is then reduced to the corresponding hydrazine derivative 4.4. The transformation can be effected by chemical reduction, for example by the use of sodium borohydride, sodium cyanoborohydride, or sodium triacetoxyborohydride or the like, or by palladium-catalyzed reduction in the presence of hydrogen or a hydrogen donor such as ammonium formate. Preferably, the hydrazone 4.3

is reduced to the hydrazine 4.4 by hydrogenation at ambient temperature and pressure, in the presence of palladium hydroxide on carbon, as described in Org. Process Res. Dev., 2002, 6, 323.

5 The preparation of the hydrazine derivatives 1.2 in which a diaryl moiety is present is shown in Scheme 4, Example 1. In this procedure, a formyl-substituted phenyl boronate 4.5 (Lancaster Synthesis) is transformed, by means of a palladium-catalyzed coupling with an aryl or heteroaryl bromide 4.6, to afford the aldehyde 4.7. The coupling of aryl bromides with aryl boronates is described, for example, in Palladium Reagents and Catalysts, by J. Tsuji, Wiley 1995, p. 218 and in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 10 57. Typically, the reactants 4.5 and 4.6 are combined in an aprotic organic solvent such as dimethylformamide in the presence of a palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium and a base such as sodium bicarbonate or potassium acetate, to afford the coupled product 4.7. This material is then reacted with a protected hydrazine derivative such as tert-butoxycarbonylhydrazine (tert-butyl carbazate) 4.2, to yield 15 the hydrazone 4.8. The reaction between equimolar amounts of the aldehyde and the protected hydrazine is conducted in alcoholic solvent such as ethanol, at reflux temperature, for example as described in WO9740029, to produce the hydrazone 4.8. The latter compound is then reduced, for example by the use of hydrogen in the presence of a palladium catalyst, as described in WO 9740029, or by the use of sodium cyanoborohydride and p-toluenesulfonic acid in tetrahydrofuran, as described in J. Med. Chem., 1998, 41, 3387, to afford the 20 substituted hydrazine 1.2. Other reactants 1.2, in which R⁴ is as defined in Chart 4, are prepared from the appropriate aldehydes, using the procedures of Scheme 4.

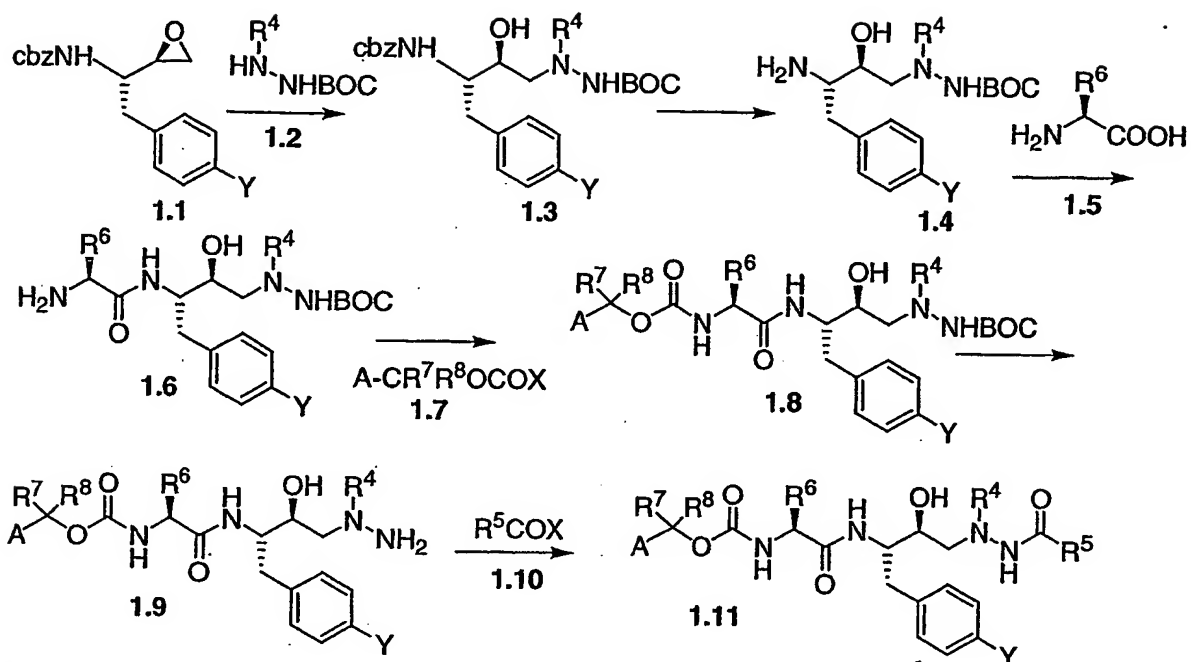
Scheme 4, Example 2 illustrates the preparation of phosphonate-containing pyridylphenyl hydrazine derivatives 4.11, which are employed in the preparation of the phosphonate esters 25 3a. In this procedure, a phosphonate-substituted pyridyl benzaldehyde 4.9, the preparation of which is described below, (Schemes 40 and 41) is reacted, as described above, with tert. butyl carbazate 4.2, to afford the hydrazone 4.10. This compound is then reduced, in the presence of palladium hydroxide as catalyst, as described above, to yield the hydrazine product 4.11. Scheme 4, Example 3 illustrates the preparation of phosphonate-containing biphenyl hydrazine 30 derivatives 4.13, which are employed in the preparation of the phosphonate esters 3b. In this procedure, a phosphonate-substituted phenyl benzaldehyde 4.12 the preparation of which is

described below, (Schemes 42- 44) is converted, as described above in Example 2 into hydrazine product 4.13.

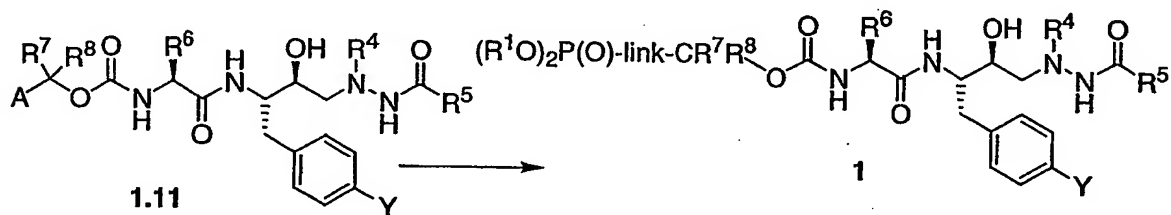
5 Scheme 4, Example 4 illustrates the preparation of phosphonate-containing phenyl hydrazine derivatives 4.15, which are employed in the preparation of the phosphonate esters 3d. In this procedure, a phosphonate-substituted phenyl benzaldehyde 4.14, the preparation of which is described below, (Schemes 45 - 48) is converted, as described above in Example 2 into hydrazine product 4.15.

10 Scheme 4, Example 5 illustrates the preparation of phosphonate-containing cyclohexyl hydrazine derivatives 4.17, which are employed in the preparation of the phosphonate esters 3c. In this procedure, a phosphonate-substituted cyclohexane carboxaldehyde 4.16, the preparation of which is described below, (Schemes 49 - 52) is converted, as described above in Example 2 into hydrazine product 4.17.

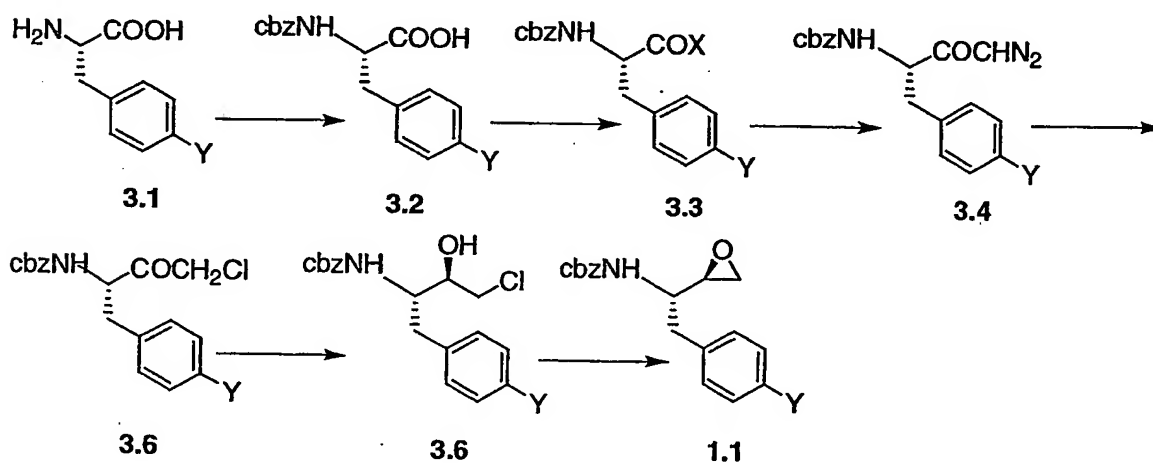
Scheme 1



Scheme 2



Scheme 3

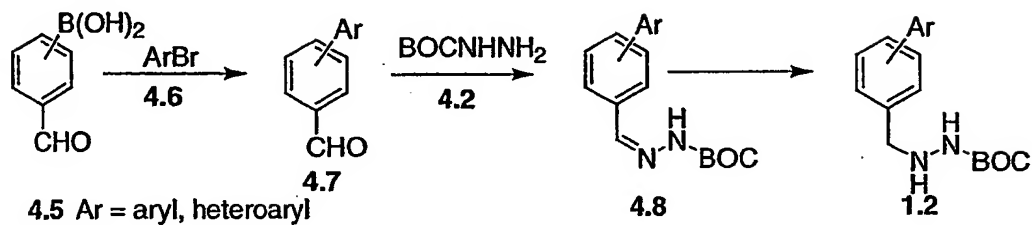


Scheme 4

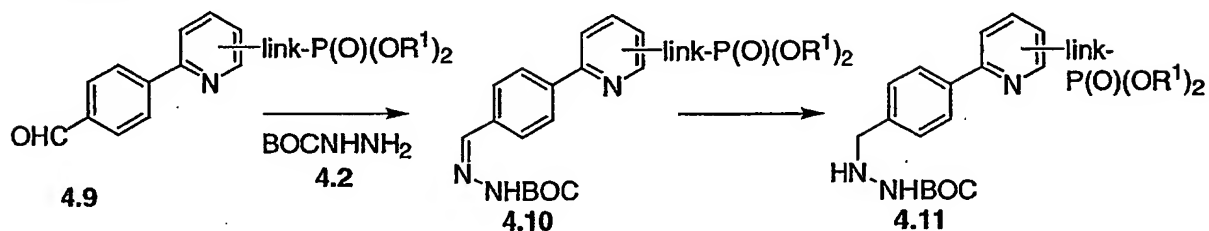
General reaction



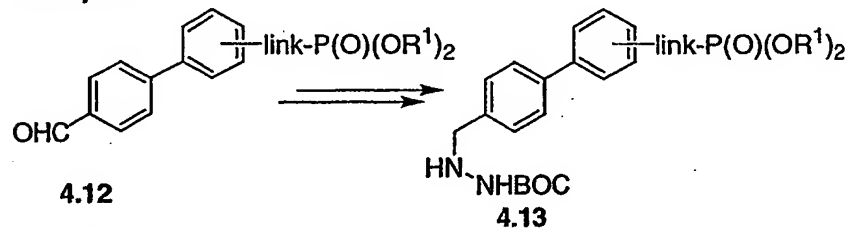
Example 1



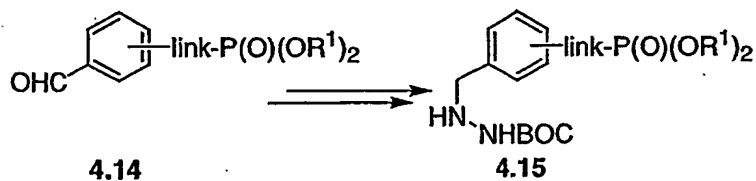
Example 2



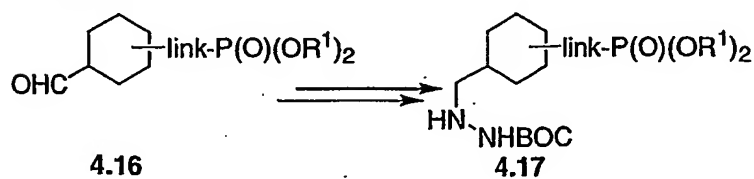
Example 3



Example 4



Example 5



Preparation of the phosphonate ester intermediates 1 in which X is sulfur.

Schemes 5 and 6 illustrate the preparation of the compounds 1 in which X is sulfur. In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, 5.1, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol R^3SH 5.2, as defined above, to afford the thioether 5.3.

The reaction is conducted in an organic solvent such as, for example, pyridine, DMF, toluene and the like, optionally in the presence of water, in the presence of an inorganic or organic base, at from 0° to 80°, for from 1-12 hours. Preferably the mesylate 5.1 is reacted with an equimolar amount of the thiol R^3SH 5.2, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°, as described in J. Org. Chem., 1994, 59, 3656, to give the product 5.3. The 1,3-dioxolane protecting group present in the compound 5.3 is then removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol 5.4. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p191. For example, the 1,3-dioxolane compound 5.3 is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane 5.3 is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°, to yield the diol product 5.4.

The primary hydroxyl group of the diol 5.4 is then selectively activated by reaction with an electron-withdrawing reagent such as, for example, dinitrobenzoyl chloride or p-toluenesulfonyl chloride. The reaction is conducted in an inert solvent such as pyridine, dichloromethane and the like, in the presence of an inorganic or organic base.

Preferably, equimolar amounts of the diol 5.4 and p-toluenesulfonyl chloride are reacted in a solvent such as pyridine, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, as described in J. Org. Chem, 2000, 65, 1623, to afford the p-toluenesulfonate ester 5.5.

The latter compound is then reacted with the hydrazine derivative 1.2 to afford the hydrazine 5.6. The displacement reaction is conducted in a polar aprotic solvent such as

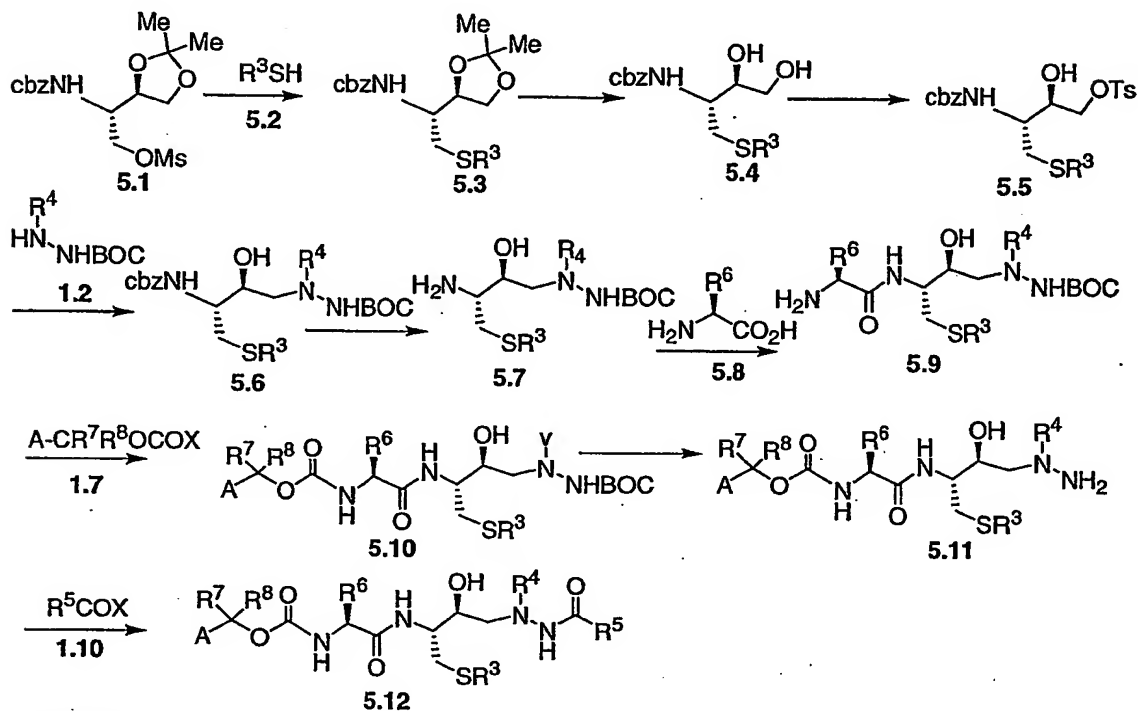
dimethylformamide, acetonitrile, dioxan and the like, in the presence of an organic or inorganic base, to afford the product 5.6. Preferably, equimolar amounts of the reactants are combined in dimethylformamide at ca. 80° in the presence of potassium carbonate, to produce the hydrazine product 5.6. The cbz protecting group is then removed to afford the amine 5.7. The removal of carbobenzyloxy substituents to afford the corresponding amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion can be effected by the use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a palladium catalyst. Alternatively, the cbz group can be removed by treatment of the substrate with triethylsilane, triethylamine and a catalytic amount of palladium (II) chloride, as described in Chem. Ber., 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient temperature, as described in J. Chem. Soc., Perkin Trans. I, 1277, 1988. The cbz group can also be removed by treatment with Lewis acid such as boron tribromide, as described in J. Org. Chem., 39, 1247, 1974, or aluminum chloride, as described in Tet. Lett., 2793, 1979. Preferably, the cbz protecting group is removed by hydrogenation of the substrate 5.6 in the presence of 5% palladium on carbon catalyst, to yield the amine 5.7. The amine is then coupled with the aminoacid 5.8 to give the amine 5.9. The reaction is effected under the same conditions as described above for the preparation of the amide 1.6.

The amine is then reacted with a reagent A-CR⁷R⁸OCOX (1.7), in which the substituent A is the group (R¹O)₂P(O)-link, or a precursor group thereto, such as [OH], [SH], [NH], Br, as described below, and in which the substituent X is a leaving group, to yield the carbamate 5.10. The reagent A-CR⁷R⁸OCOX is derived from the corresponding alcohol A-CR⁷R⁸OH, using methods described below, (Scheme 20). The preparation of the reactants A-CR⁷R⁸OCOX is described in Schemes 21 - 26. The preparation of carbamates by means of reactions between alcohols and amines is described below, in Scheme 20.

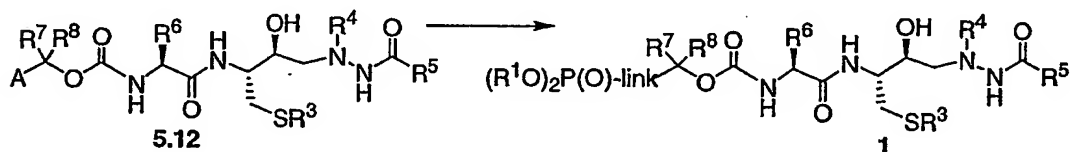
The BOC protecting group is then removed from the product 5.10 to produce the hydrazine 5.11. The conditions for the removal of the BOC group are the same as those described above (Scheme 1). The product is then acylated with the carboxylic acid or activated derivative thereof, 1.10, using the conditions described above, (Scheme 1) to yield the product 5.12. The procedures illustrated in Scheme 5 depict the preparation of the compounds 5.11 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 6 illustrates the conversion of compounds 5.12 in which

A is a precursor to the group $\text{link-P(O)(OR}^1)_2$ into the compounds 1. Procedures for the conversion of the substituent A into the group $\text{link-P(O)(OR}^1)_2$ are illustrated below, (Schemes 21 - 56).

Scheme 5



Scheme 6



5

Preparation of the phosphonate ester intermediates 2 in which X is a direct bond.

- 10 Schemes 7 and 8 illustrate the preparation of the phosphonate esters 2 in which X is a direct bond. As shown in Scheme 7, a cbz-protected oxirane 7.1 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br, is reacted with a hydrazine derivative 1.2, to afford the ring-opened product 7.3. The conditions for the reaction are the same as those described above for the preparation of the hydrazine derivative

1.3, (Scheme 1). The preparation of the substituted oxiranes 7.1 are described below, in Scheme 9. The product 7.3 is then transformed, using the sequence of reactions illustrated in Scheme 7, into the product 7.8. The conditions employed for the component reactions of this sequence are the same as for the analogous reaction in Scheme 1.

5

The procedures illustrated in Scheme 7 depict the preparation of the compounds 7.8 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 8 illustrates the conversion of compounds 7.8 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 2. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 21 - 56).

10

Scheme 9 illustrates the preparation of the oxiranes 7.1. In this sequence, a substituted phenylalanine 9.1, in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below, is transformed into the cbz-protected derivative 9.2, using the conditions described above for the preparation of the cbz derivative 3.2, (Scheme 3). The latter compound is then transformed, using the sequence of reactions illustrated in Scheme 3, into the product 7.1. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme 3.

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Preparation of the phosphonate ester intermediates 2 in which X is a sulfur.

Schemes 10 and 11 illustrate the preparation of the compounds 2 in which X is sulfur. As shown in Scheme 10, the mesylate 5.1 is reacted with the substituted thiophenol 10.1, in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below (scheme 30-39), to afford the thioether 10.2. The conditions employed for this reaction are the same as those described above for the preparation of the thioether 5.3, Scheme 5. The product 10.2 is then transformed, using the series of reactions shown in Scheme 5, into the diacylated thioether 10.3. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme 5.

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The procedures illustrated in Scheme 10 depict the preparation of the compounds 10.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as

[OH], [SH] Br, as described below. Scheme 11 illustrates the conversion of compounds 10.3 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 2. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 21 - 56).

Preparation of the phosphonate ester intermediates 3 in which X is a direct bond.

Schemes 12 and 13 depict the preparation of the phosphonate esters 3a in which X is a direct bond. As shown in Scheme 12, the oxirane 1.1 is reacted with a BOC protected phenylhydrazine derivative 12.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. The preparation of the hydrazine derivatives 12.1 is described in Schemes 4, 40 and 41. The reaction is conducted under the same conditions as described above for the preparation of the hydrazine 7.3, Scheme 7. The product 12.2 is then transformed, using the sequence of reactions shown in Scheme 7 for the transformation of the hydrazine 7.3 into the diacylated compound 7.8, into the diacylated compound 12.3. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme 7.

The procedures illustrated in Scheme 12 depict the preparation of the phosphonate esters 12.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 13 illustrates the conversion of compounds 12.3 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 3a in which X is a direct bond. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 21 - 56).

The phosphonate esters 3b, 3c and 3d, in which X is a direct bond, are prepared using the procedures of Schemes 12 and 13, except that the hydrazine derivatives 4.13, 4.17 and 4.15, prepared as described in Schemes 42 - 52, are used in place of the hydrazine derivative 12.1.

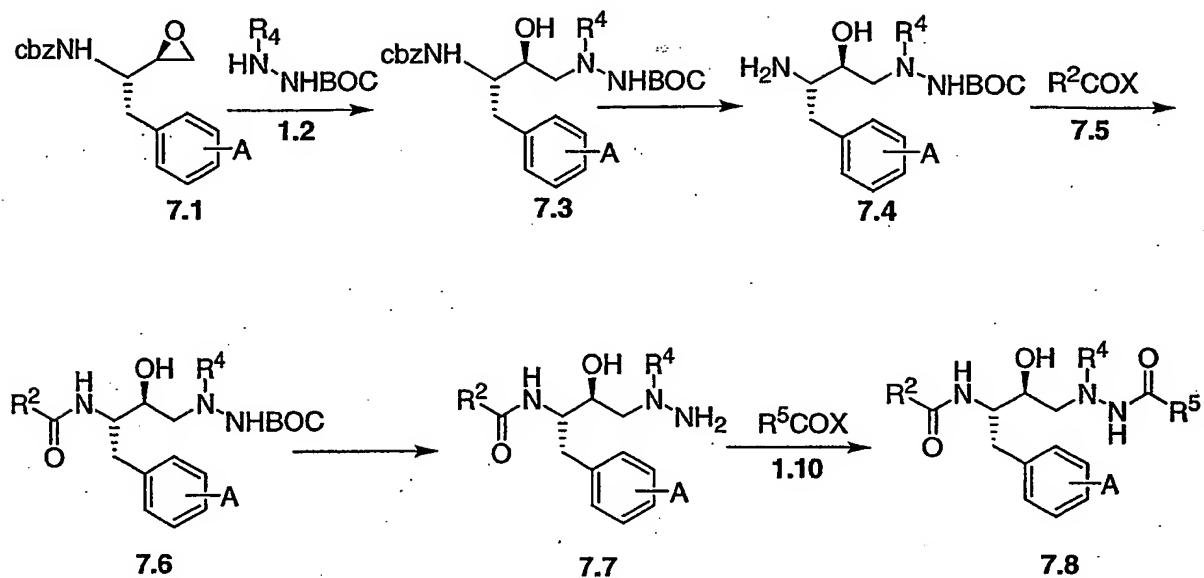
Preparation of the phosphonate ester intermediates 3 in which X is sulfur.

Schemes 14 and 15 illustrate the preparation of the phosphonate esters 3a in which X is sulfur.

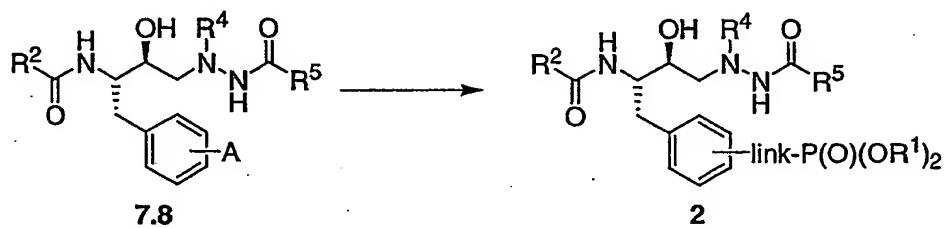
- 5 As shown in Scheme 14, the p-toluenesulfonate ester 5.5 is reacted with the phenylhydrazine derivative 12.1, in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, to afford the hydrazine derivative 14.1. The reaction is conducted under the same conditions as described above for the preparation of the hydrazine 5.6, Scheme 5. The product 14.1 is then transformed into the diacylated
- 10 product 14.2, using the sequence of reactions shown in Scheme 5. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme 5. The procedures illustrated in Scheme 14 depict the preparation of the phosphonate esters 14.2 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 15 illustrates the conversion of compounds 14.2
- 15 in which A is a precursor to the group $\text{link-P(O)(OR}^1)_2$ into the compounds 3a in which X is S. Procedures for the conversion of the substituent A into the group $\text{link-P(O)(OR}^1)_2$ are illustrated below, (Schemes 21 - 56).

- The phosphonate esters 3b, 3c and 3d, in which X is S, are prepared using the procedures of Schemes 12 and 13, except that the hydrazine derivatives 4.13, 4.17 and 4.15, prepared as
- 20 described in Schemes 42 - 52, are used in place of the hydrazine derivative 12.1.

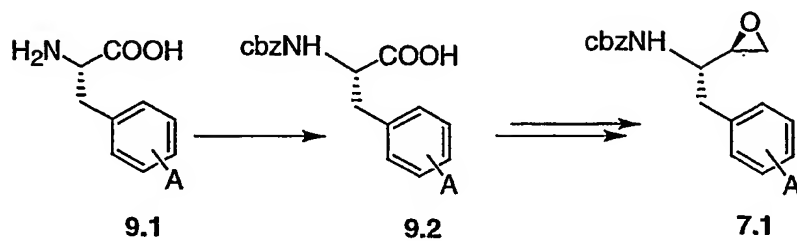
Scheme 7



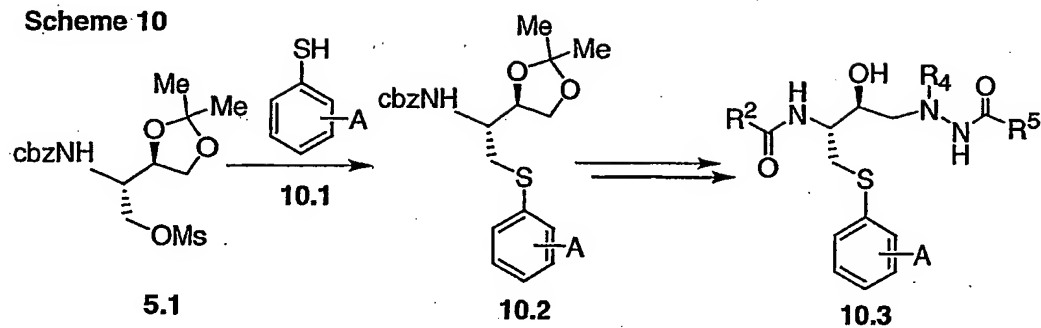
Scheme 8



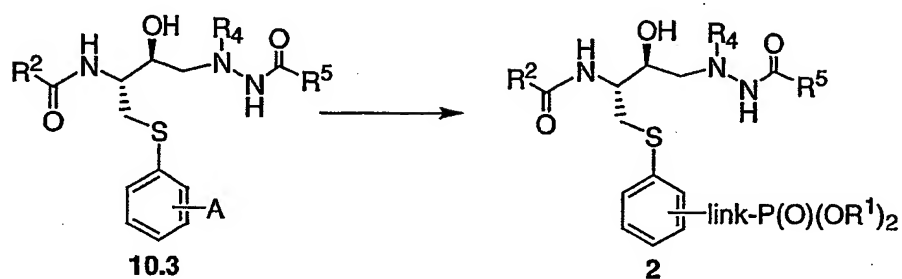
Scheme 9



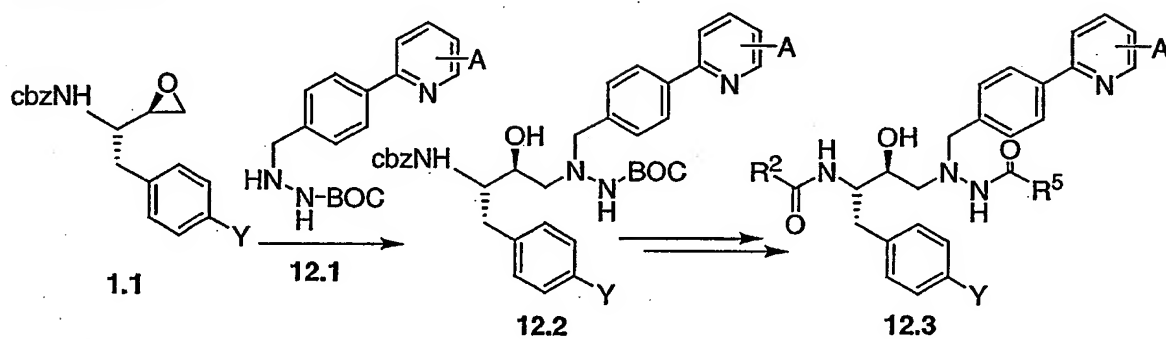
Scheme 10



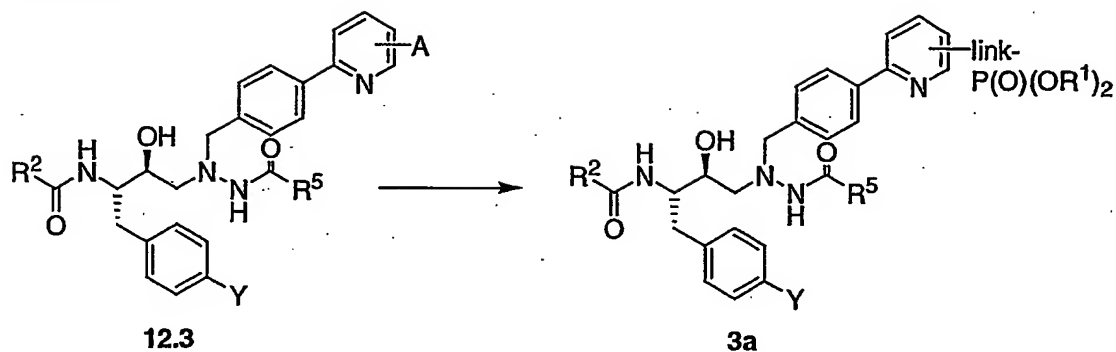
Scheme 11



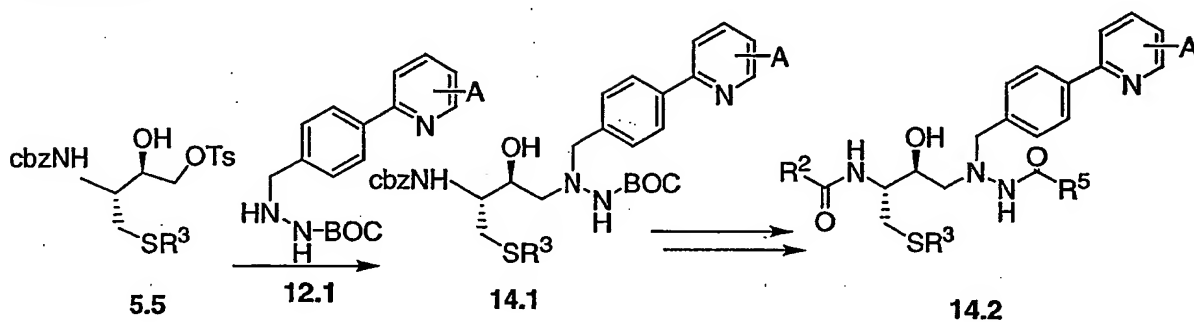
Scheme 12



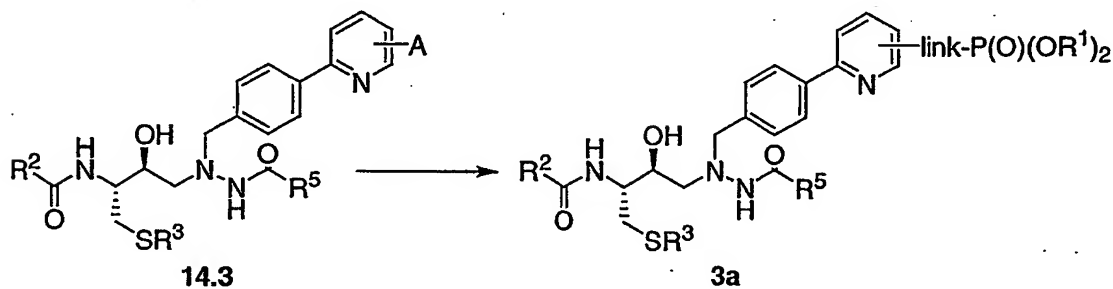
Scheme 13



Scheme 14



Scheme 15



Preparation of the phosphonate ester intermediates 4 in which X is a direct bond.

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Schemes 16 and 17 illustrate the preparation of the phosphonate esters 4 in which X is a direct bond. As shown in Scheme 16, the amine 1.4, prepared as described in Scheme 1, is reacted with the carboxylic acid or activated derivative thereof R^2COX 7.5, to afford the amide 16.1. The conditions for the amide forming reaction are the same as those described above for the

preparation of the amide 1.11, (Scheme 1). The product is then deprotected by removal of the BOC group, using the procedures described above (Scheme 1), to yield the hydrazine 16.2.

This material is then coupled with the aminoacid 1.5, using the coupling procedures described above for the preparation of the amide 1.6, to produce the amide 16.3. The product is then
5 reacted with the acylating agent $A-CR^7R^8OCOX$, 1.7, in which A and X are as described above, Scheme 1, to afford the carbamate product 16.4.

The procedures illustrated in Scheme 16 depict the preparation of the phosphonate esters 16.4 in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 17 illustrates the conversion of compounds 16.4
10 in which A is a precursor to the group $link-P(O)(OR^1)_2$ into the compounds 4. Procedures for the conversion of the substituent A into the group $link-P(O)(OR^1)_2$ are illustrated below, (Schemes 21 - 56).

Preparation of the phosphonate ester intermediates 4 in which X is sulfur.

Schemes 18 and 19 illustrate the preparation of the phosphonate esters 4 in which X is sulfur. As shown in Scheme 18, the amine 5.7, prepared as described in Scheme 5, is reacted with the carboxylic acid or activated derivative thereof 7.5, to produce the amide 18.1. The reaction is performed under the conditions described above for the preparation of the amide 1.11. The
20 BOC group present in the amide 18.1 is then removed using the procedures described above, (Scheme 1) to afford the amine 18.2. This material is then coupled with the aminoacid 1.5, using the procedures described above for the preparation of the amide 1.6, to produce the amide 18.3. The latter compound is then reacted with the acylating agent $A-CR^7R^8OCOX$, 1.7, in which A and X are as described above, Scheme 1, to afford the carbamate product
25 18.4.

The procedures illustrated in Scheme 18 depict the preparation of the phosphonate esters 18.4 in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 19 illustrates the conversion of compounds 18.4 in which A is a precursor to the group $link-P(O)(OR^1)_2$ into the compounds 4. Procedures for
30 the conversion of the substituent A into the group $link-P(O)(OR^1)_2$ are illustrated below, (Schemes 21 - 56).

Preparation of the phosphonate ester intermediates 5 in which X is a direct bond.

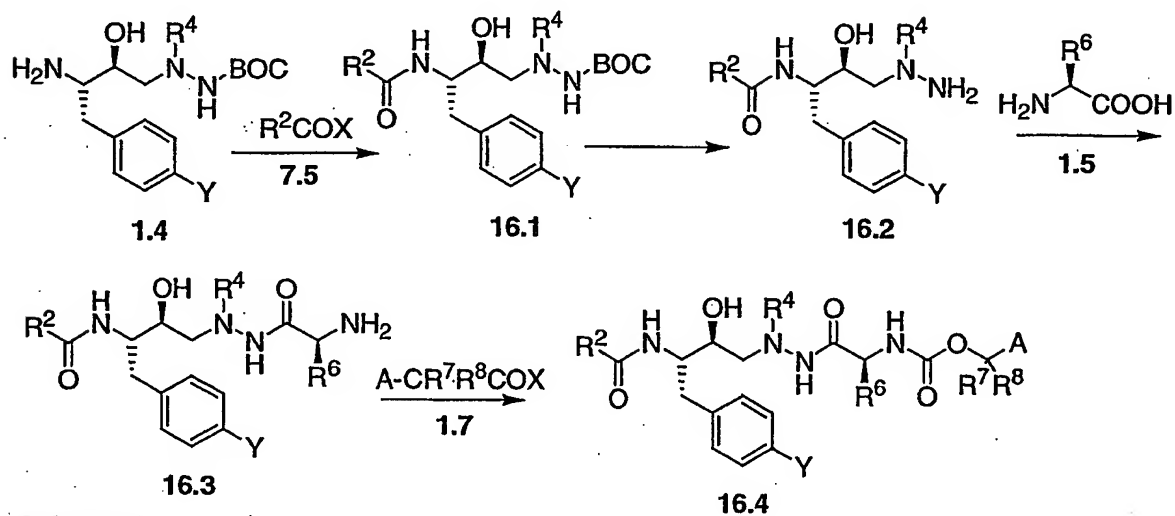
Schemes 19a and 19b illustrate the preparation of the phosphonate esters 5 in which X is a direct bond. As shown in Scheme 19a, the amine 1.6 is reacted with a quinoline-2-carboxylic acid derivative 19a.1, in which the substituent A is either the group $(R^1O)_2P(O)$ -link or a precursor group thereto, such as OH, SH, Br to afford the amide 19a.2. The reaction is performed as described above for the preparation of the amide 1.6 (Scheme 1). The BOC protecting group is then removed, using the procedures described in Scheme 1, to yield the amine 19a.3. This compound is then reacted, as described above, with the carboxylic acid R^5COOH , or an activated derivative thereof 19a.4, to give the amide 19a.5. The procedures illustrated in Scheme 19a depict the preparation of the phosphonate esters 19a.5 in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 19b illustrates the conversion of compounds 19a.5 in which A is a precursor to the group link- $P(O)(OR^1)_2$ into the compounds 5. Procedures for the conversion of the substituent A into the group link- $P(O)(OR^1)_2$ are illustrated below, (Schemes 21 - 56). The preparation of the quinoline carboxylic acid reagents 19a.1 is described below, (Schemes 53 - 56).

Preparation of the phosphonate ester intermediates 5 in which X is sulfur.

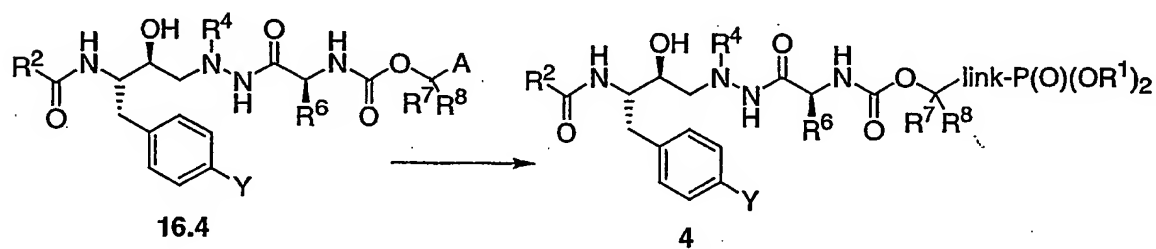
Schemes 19c and 19d illustrate the preparation of the phosphonate esters 5 in which X is sulfur. As shown in Scheme 19c, the amine 5.9 is reacted, as described above, with the quinoline carboxylic acid derivative 19a.1 to yield the amide product 19c.1. The BOC protecting group is then removed, as described above, to give the amine 19c.2. The latter compound is then reacted, as described above, with the carboxylic acid R^5COOH , or an activated derivative thereof 19a.4, to give the amide 19c.3. The procedures illustrated in Scheme 19c depict the preparation of the phosphonate esters 19c.3 in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 19d illustrates the conversion of compounds 19c.3 in which A is a precursor to the group link- $P(O)(OR^1)_2$ into the compounds 5. Procedures for the conversion of the substituent A into the group link- $P(O)(OR^1)_2$ are

illustrated below, (Schemes 21 - 56). The preparation of the quinoline carboxylic acid reagents **19a.1** is described below, (Schemes 53 - 56).

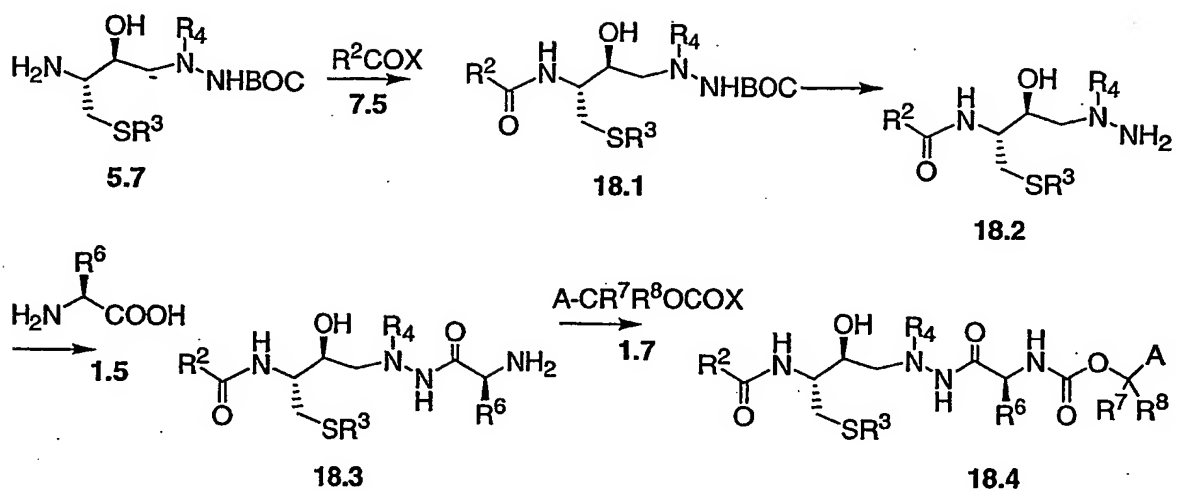
Scheme 16



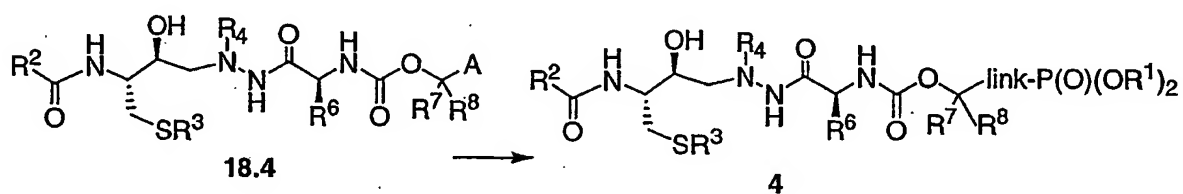
Scheme 17



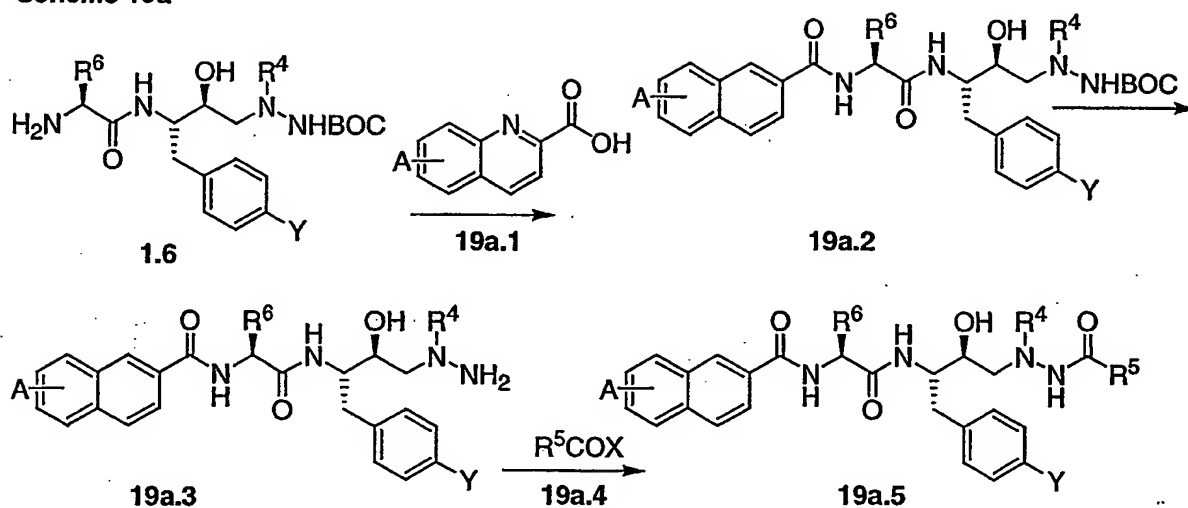
Scheme 18



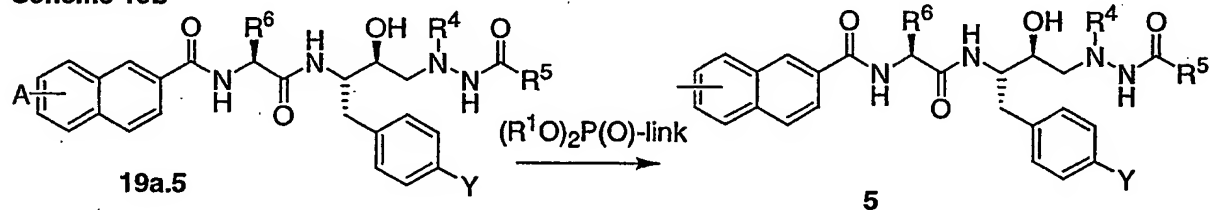
Scheme 19



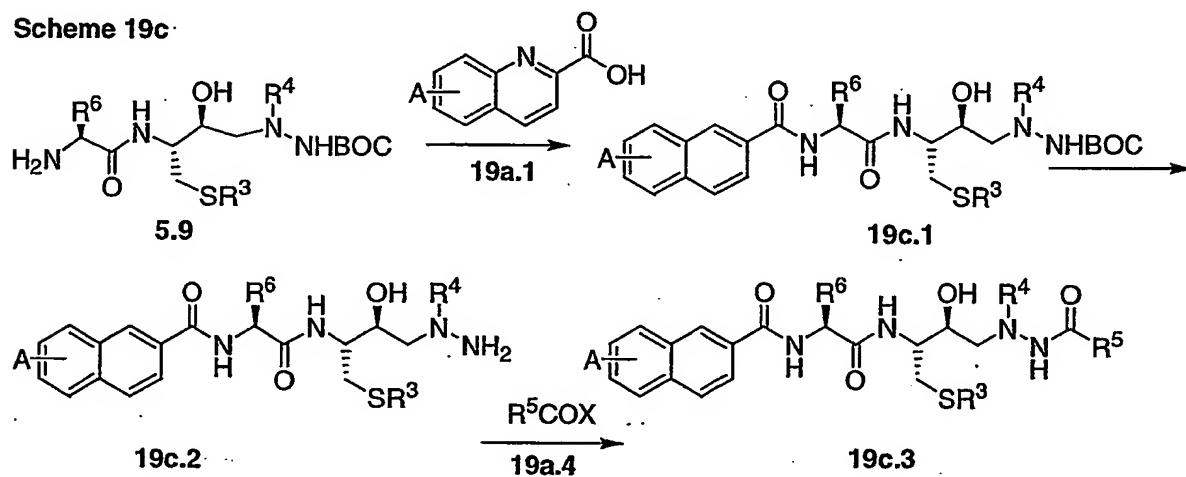
Scheme 19a



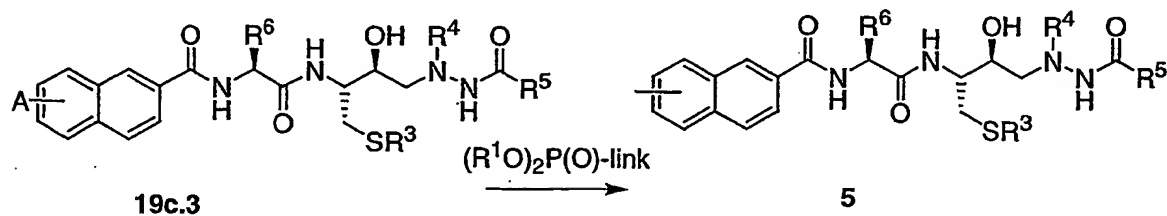
Scheme 19b



Scheme 19c



Scheme 19d



Preparation of carbamates.

The phosphonate esters 1 and 4, and the phosphonate ester 1-7 in which the R²CO or R⁵CO groups are formally derived from the carboxylic acids C38 - C49 (Chart 2c) contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme 20 illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme 20, in the general reaction generating carbamates, a carbinol 20.1, is converted into the activated derivative 20.2 in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative 20.2 is then reacted with an amine 20.3, to afford the carbamate product 20.4. Examples 1 - 7 in Scheme 20 depict methods by which the general reaction can be effected. Examples 8 - 10 illustrate alternative methods for the preparation of carbamates.

Scheme 20, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol 20.5. In this procedure, the carbinol 20.5 is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate 20.6. The latter compound is then reacted with the amine component 20.3, in the presence of an organic or inorganic base, to afford the carbamate 20.7. For example, the chloroformyl compound 20.6 is reacted with the amine 20.3 in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate 20.7. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 20, Example 2 depicts the reaction of the chloroformate compound 20.6 with imidazole to produce the imidazolide 20.8. The imidazolide product is then reacted with the amine 20.3 to yield the carbamate 20.7. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is

conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 20 Example 3, depicts the reaction of the chloroformate 20.6 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 20.10. The reaction is

5 conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 20.19 - 20.24 shown in Scheme 20, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 20.19, N-hydroxysuccinimide 20.20, or pentachlorophenol, 20.21, the mixed carbonate 20.10 is obtained by the reaction of the
10 chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 20.22 or 2-hydroxypyridine 20.23 can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

15 Scheme 20 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 20.8 is employed. In this procedure, a carbinol 20.5 is reacted with an equimolar amount of carbonyl diimidazole 20.11 to prepare the intermediate 20.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 20.8 is then reacted with an equimolar amount of the
20 amine R'NH₂ to afford the carbamate 20.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 20.7.

Scheme 20, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxy carbonylbenztriazole 20.13. In this procedure, a carbinol ROH is reacted at ambient
25 temperature with an equimolar amount of benztriazole carbonyl chloride 20.12, to afford the alkoxy carbonyl product 20.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. The product is then reacted with the amine R'NH₂ to afford the carbamate 20.7. The reaction is conducted in toluene or ethanol, at from ambient temperature
30 to about 80° as described in Syn., 1977, 704.

Scheme 20, Example 6 illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, 20.14, is reacted with a carbinol 20.5 to afford the intermediate alkyloxycarbonyl

intermediate 20.15. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate 20.7. The procedure in which the reagent 20.15 is derived from hydroxybenztriazole 20.19 is described in Synthesis, 1993, 908; the procedure in which the reagent 20.15 is derived from N-hydroxysuccinimide 20.20 is described in Tet. Lett., 1992, 2781; the procedure in which the reagent 20.15 is derived from 2-hydroxypyridine 20.23 is described in Tet. Lett., 1991, 4251; the procedure in which the reagent 20.15 is derived from 4-nitrophenol 20.24 is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate 20.14 is conducted in an inert organic solvent at ambient temperature.

10 Scheme 20, Example 7 illustrates the preparation of carbamates from alkoxycarbonyl azides 20.16. In this procedure, an alkyl chloroformate 20.6 is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide 20.16. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 20.7. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

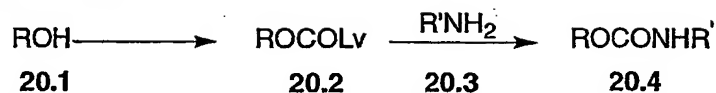
Scheme 20, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine 20.17. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate 20.7.

25 Scheme 20, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate 20.18. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate 20.7.

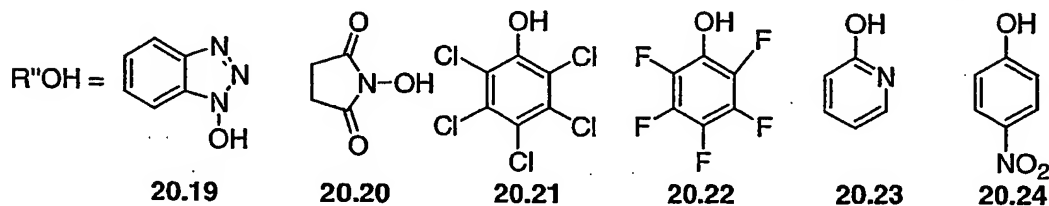
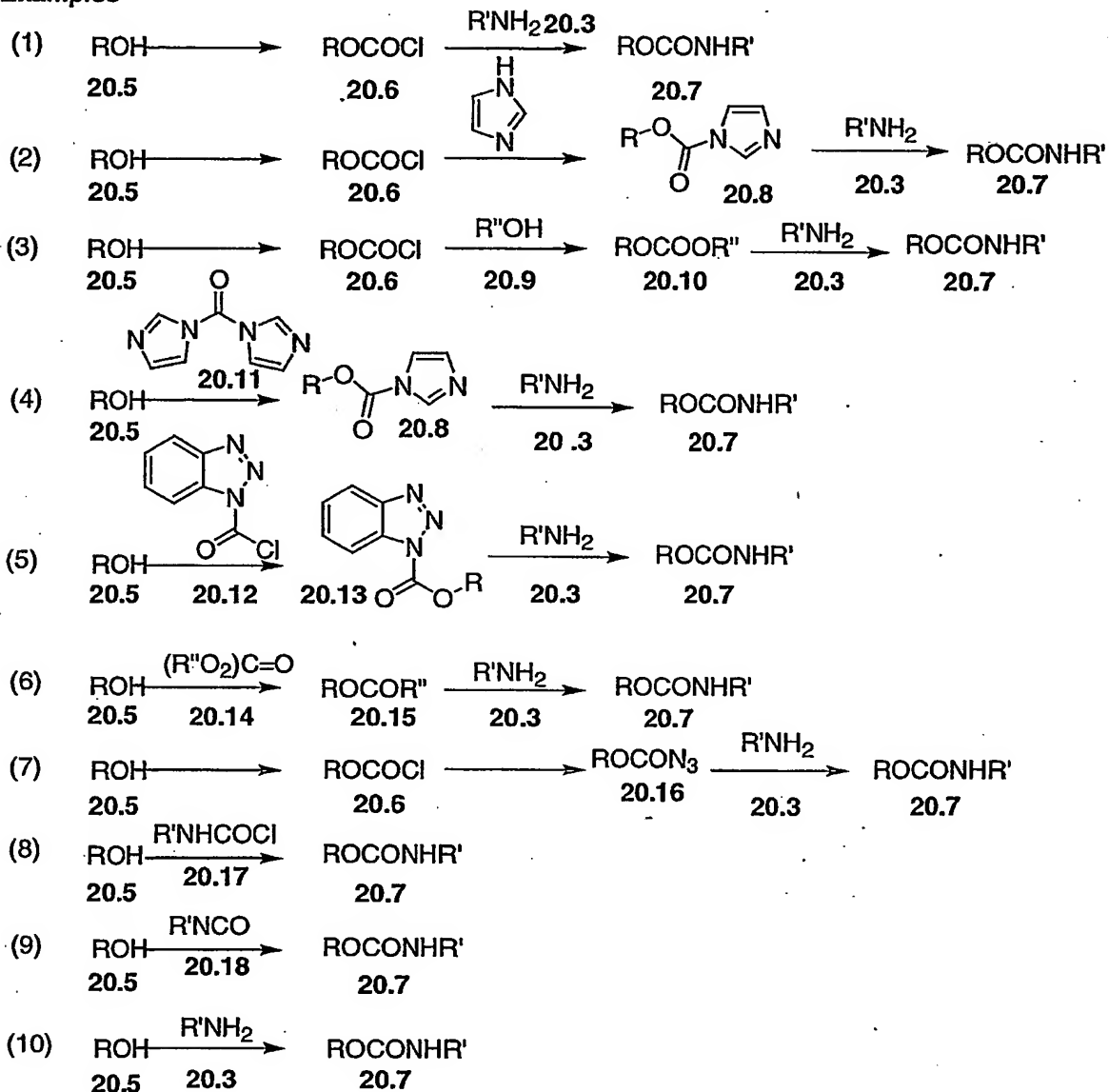
30 Scheme 20, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate 20.7.

Scheme 20

General reaction



Examples



Preparation of the reagents A-CR⁷R⁸OCOX.

The reagents A-CR⁷R⁸OCOX 1.7 are prepared from the corresponding carbinols A-CR⁷R⁸OH, using procedures such as those described above in Scheme 20. Examples of the preparation of the carbinols A-CR⁷R⁸OH and the derived reagents 1.7 are shown below in Schemes 21-26. The activation methods for the conversion of the carbinols A-CR⁷R⁸OH to the reagents A-CR⁷R⁸OCOX are interchangeable between the different alcohols A-CR⁷R⁸OH.

10 Scheme 21 depicts the preparation of phosphonate-containing reagents 21.2 in which the phosphonate is linked by means of an alkylene chain. In this procedure, a dialkyl hydroxyalkyl phosphonate 21.1 is reacted with phosgene, or an equivalent reagent, to afford the chloroformate 21.2, as described above in Scheme 20, Example 1. The reaction is conducted in an inert organic solvent such as dichloromethane or toluene, at from about 0° to ambient
15 temperature.

For example, as shown in Scheme 21, Example 1, a dialkyl hydroxymethylphosphonate 21.3 (Aldrich) is reacted with excess phosgene in toluene at 0°, as described in Org. Syn. Coll. Vol. 3, 197, 1965, to afford the chloroformyl product 21.4.

Scheme 21, Example 2 illustrates the analogous conversion of a dialkyl hydroxyethyl phosphonate 21.5 (Aldrich) into the chloroformate derivative 21.6. The reaction is performed as described above for the preparation of the chloroformate 21.4.
20

Scheme 21, Example 3 illustrates the analogous conversion of a dialkyl phosphono-substituted tert. butanol 21.7, prepared as described in Fr.2462440, into the chloroformate derivative 21.8. The reaction is performed as described above for the preparation of the chloroformate
25 21.4.

Using the above procedures, but employing, in place of the phosphonates 21.3, 21.5 or 21.7, different dialkyl hydroxyalkyl phosphonates 21.1, the corresponding products 21.2 are obtained.

30 Scheme 22 depicts the preparation of phosphonate-containing reagents 22.2 in which the phosphonate is linked by means of a phenyl ring. In this procedure, a dialkyl

hydroxyalkylphenyl phosphonate 22.1 is converted, as described above, into an activated chloroformyl derivative 22.2, using the procedures described above in Scheme 20.

For example, a dialkyl 4-hydroxymethylphenylphosphonate 22.3 (Aldrich) is reacted in tetrahydrofuran with an equimolar amount of the 2-pyridyl carbonate 22.4, prepared as described in Tet. Let., 1991, 4251, to afford the product 22.5.

Using the above procedure, but employing, in place of a dialkyl hydroxyphenylphosphonate 22.3, different dialkyl hydroxyphenyl phosphonates 22.1, the corresponding products 22.2 are obtained.

10 Scheme 23 depicts the preparation of phosphonate containing reagents 23.4 in which the phosphonate group is linked by means of an alkylene chain incorporating a heteroatom O, S or N. In this procedure, a dialkyl hydroxy-, thio- or alkylaminoalkylphosphonate 23.1 is alkylated by reaction with a bromoalkanol 23.2. The alkylation reaction is conducted at from ambient temperature to about 70° in a polar organic solvent such as dimethylformamide, 15 dioxan or acetonitrile, in the presence of a base. In cases in which X is oxygen, a strong base such as lithium hexamethyldisilylazide or potassium tert-butoxide is employed. In cases in which X is sulfur or alkylamino, an inorganic base such as potassium carbonate or cesium carbonate is used. The product 23.3 is then converted into an activated derivative 23.4 by means of one of the methods described above in Scheme 20.

20 For example, as shown in Scheme 23, Example 1, a dialkyl 2-mercaptoethylphosphonate 23.5, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, is reacted with one molar equivalent of bromoethanol 23.6, in dimethylformamide at 60° in the presence of cesium carbonate, to afford the thioether product 23.7. This compound is then reacted with pentafluorophenyl carbonate 23.8, (Fluorochem) in dimethylformamide solution at ambient 25 temperature in the presence of triethylamine, to afford the pentafluorophenoxycarbonyl product 23.9.

As a further example of the method of Scheme 23, as shown in Example 2, a dialkyl methylaminomethyl phosphonate 23.10, (AsInEx Inc.) is reacted in dimethylformamide at 70° with one molar equivalent of 5-bromo-2-hydroxy-2-methylpentane 23.11, prepared as 30 described in J. Med. Chem., 1994, 37, 2343, and potassium carbonate, to afford the amine product 23.12. The product is then converted, as described above, into the pentafluorophenyl formate derivative 23.13.

Using the above procedures, but employing, in place of a dialkyl 2-mercaptoethylphosphonate 23.5, or a dialkyl methylaminomethyl phosphonate 23.10, different hydroxy, mercapto or aminoalkylphosphonates 23.1, and/or different bromoalkanols 23.2, and/or different activation methods, the corresponding products 23.4 are obtained.

5

Scheme 24 illustrates the preparation of phosphonate containing reagents 24.4 in which the phosphonate group is linked by means of an alkylene chain incorporating an N-alkyl group. In this procedure, a dialkyl formylalkyl phosphonate 24.1 is reacted with an alkylaminoalkanol 24.2 under reductive amination conditions, so as to afford the product 24.3. The preparation of amines by means of reductive amination procedures is described, for example, in
10 Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this reaction, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride,
15 sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The reduction reaction can also be performed by hydrogenation in the presence of a palladium catalyst and hydrogen or a hydrogen donor. The reaction product 24.3 is then transformed into the activated derivative 24.4 by means of one of the procedures described above in
20 Scheme 20.

As shown in Scheme 24, Example 1, a dialkyl formylmethylphosphonate 24.5 (Aurora) is reacted with methylaminoethanol 24.6, in the presence of sodium cyanoborohydride, to afford the coupled product 24.7. This compound is then reacted with an equimolar amount of chlorocarbonylbenztriazole 20.13, in toluene at 80°, in the presence of one molar equivalent of
25 triethylamine, as described in Syn., 1977, 704, to yield the product 24.8.

As a further example of the method of Scheme 24, as shown in Example 2, the aldehyde 24.5 is reacted with 2-hydroxy-2-methyl-3-methylaminopropane 24.10, under reductive amination conditions, to afford the amine product 24.11. The latter compound is then reacted with phosgene, or an equivalent thereof, as described above, to afford the chloroformyl product
30 24.12.

Using the above procedures, but employing, in place of the phosphonates 24.5, different phosphonates 24.1, and/or in place of the aminoalkanols 24.6 or 24.10, different

aminoalkylalkanols 24.2, and/or different activation methods described in Scheme 20, the corresponding products 24.4 are obtained.

5 Scheme 25 illustrates the preparation of phosphonate containing reagents 25.2 in which the phosphonate group is linked by means of an alkylene chain incorporating an acetylenic linkage. In this procedure, a dialkyl hydroxyalkynyl phosphonate 25.1 is converted, by means of one of the procedures described in Scheme 20, into the activated formyl derivative 25.2.

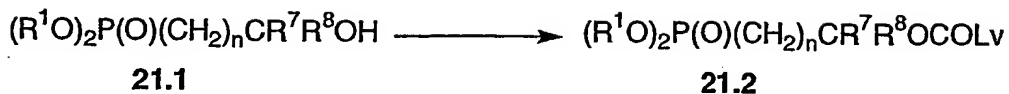
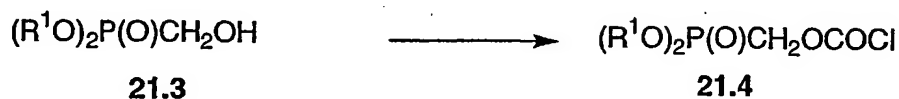
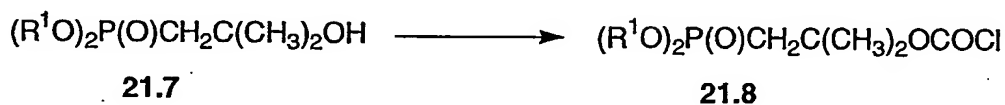
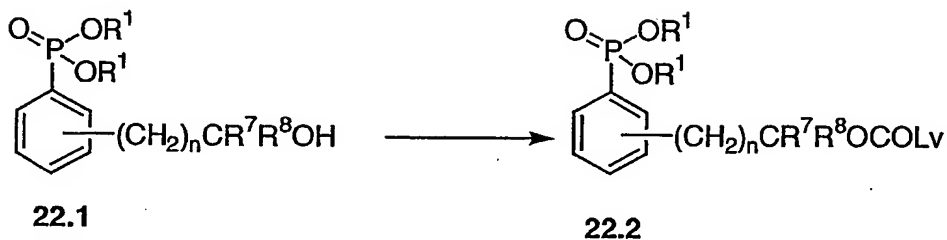
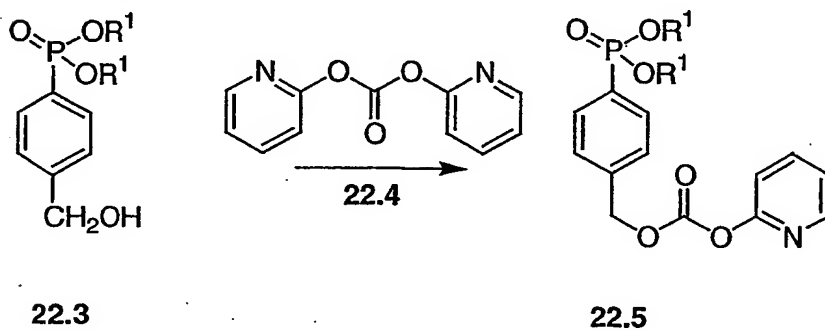
For example, a dialkyl hydroxypropynyl phosphonate 25.3 prepared as described in J. Org. Chem., 1987, 52, 4810, is reacted with one molar equivalent of di(succinimidyloxy)carbonate 10 25.4, prepared as described in Tet. Lett, 1992, 2781, in dichloromethane at ambient temperature, to afford the product 25.5.

Using the above procedures, but employing, in place of the dialkyl hydroxypropynyl phosphonate 25.3, different dialkyl hydroxyalkynyl phosphonates 25.1, the corresponding products 25.2 are obtained.

15 Scheme 26 illustrates the preparation of phosphonate containing reagents 26.2 in which the phosphonate group is linked by means of an alkylene chain incorporating an olefinic linkage. In this procedure, a dialkyl hydroxyalkenyl phosphonate 26.1 is converted, by means of one of the procedures described in Scheme 20, into the activated formyl derivative 26.2.

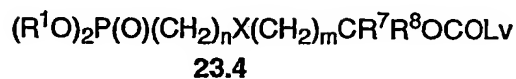
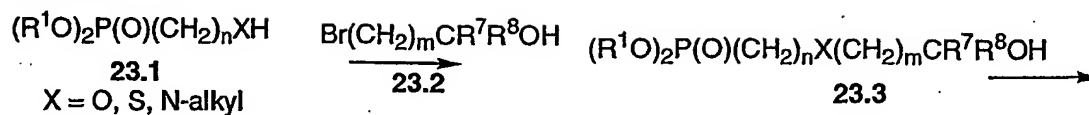
20 For example, a dialkyl propenylphosphonate 26.3, prepared as described in Zh. Obschei. Khim., 1974, 44, 18343, is reacted with phosgene in toluene at 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to afford the chloroformyl product 26.4.

Using the above procedures, but employing, in place of the dialkyl hydroxypropenyl phosphonate 26.3, different dialkyl hydroxyalkenyl phosphonates 26.1, the corresponding 25 products 26.2 are obtained.

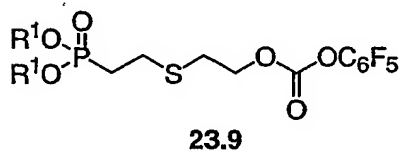
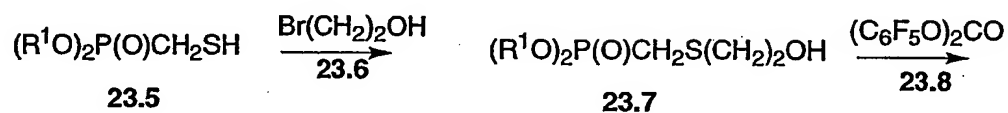
Scheme 21**Method****Example 1****Example 2****Example 3****Scheme 22****Method****Example**

Scheme 23

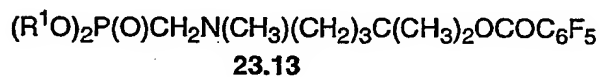
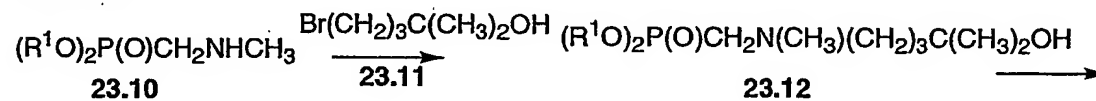
Method



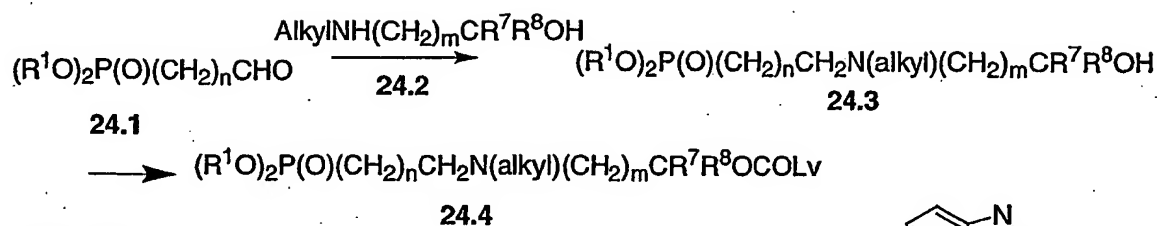
Example 1



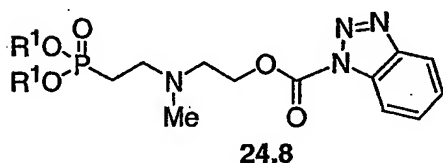
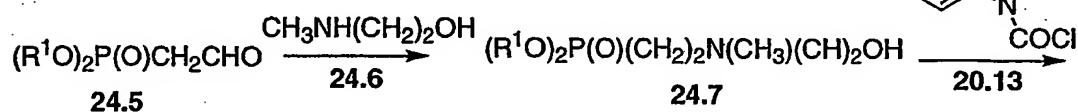
Example 2



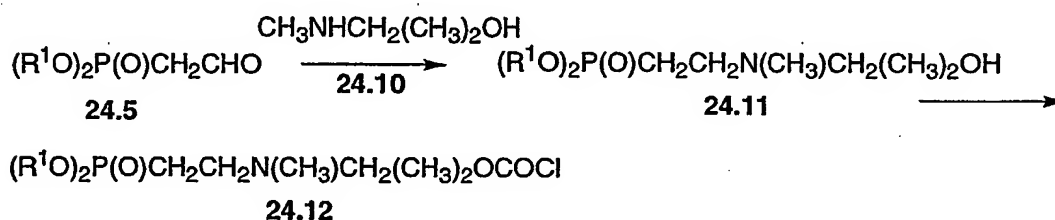
Scheme 24
Method



Example 1

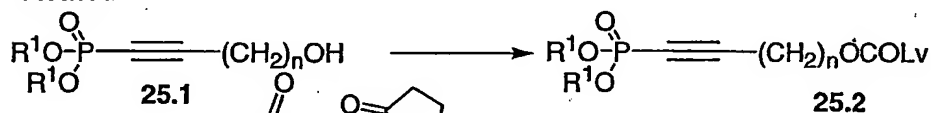


Example 2

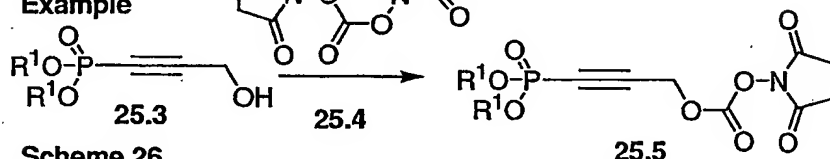


Scheme 25

Method

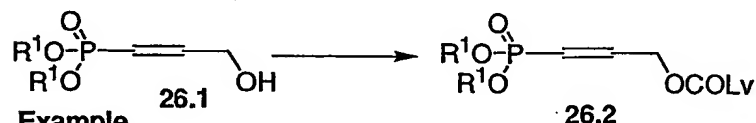


Example

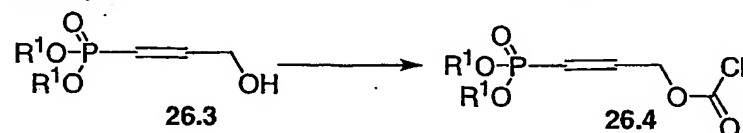


Scheme 26

Method



Example



Preparation of the oxirane reactants 7.1.

5 The oxirane reactants 7.1 are obtained by means of chemical transformations applied to variously substituted phenylalanine derivatives. In the methods described below, the phosphonate moiety can be introduced into the molecule at any appropriate stage in the synthetic sequence, or after the intermediates are incorporated into the phosphonate esters 2.

10 Scheme 27 depicts the preparation of oxirane reactants 27.5 in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine 27.1 is converted into the cbz-protected derivative, using the procedures described above in Scheme 3. The protected product 27.2 is then converted, by means of the series of reactions shown in Scheme 3, into the oxirane 27.3. The latter compound is then reacted with a dialkyl phosphite 27.4, in the presence of a palladium catalyst, to afford the phosphonate ester 27.5. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.

For example, 4-bromophenylalanine 27.6, prepared as described in Biotech. Lett., 1994, 16, 373, is converted, as described above, (Scheme 3), into the oxirane 27.7. This compound is then reacted, in toluene solution at reflux, with a dialkyl phosphite 27.4, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 27.8.

Using the above procedures, but employing, in place of 4-bromophenylalanine 27.6, different bromo-substituted phenylalanines 27.1, and/or different dialkyl phosphites, the corresponding products 27.5 are obtained.

Scheme 28 illustrates the preparation of oxiranes 28.4 in which the phosphonate moiety is attached by means of an alkylene chain. In this procedure, a carbobenzyloxy protected bromo-substituted phenylalanine 27.2, prepared as described above, is coupled, in the presence of a palladium catalyst, with a dialkyl alkenylphosphonate 28.1, to afford the coupled product 28.2. The preparation of aryl alkenyl phosphonates by means of a coupling reaction between aryl bromides and alkenyl phosphonates is described in Syn., 1983, 556. The reaction is performed

in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a palladium (II) catalyst, a tertiary base such as triethylamine and a phosphine such as triphenylphosphine and the like, to afford the aryl alkenyl phosphonate product 28.2. The latter compound is then reduced, for example by reaction with diimide, as described in
5 Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 262, to afford the saturated product 28.3. The latter compound is then converted, by means of the series of reactions shown in Scheme 3, into the oxirane 28.4.

For example, the cbz-protected 3-bromophenylalanine 28.5, prepared as described in Pept. Res., 1990, 3, 176, is coupled, in acetonitrile solution at 100° in a sealed tube, with a dialkyl
10 vinylphosphonate 28.6, in the presence of palladium (II)acetate, tri-(o-tolyl)phosphine and triethylamine, as described in Syn., 1983, 556, to afford the coupled product 28.7. The product is then reduced with diimide, generated by treatment of disodium azodicarboxylate with acetic acid, as described in J. Am. Chem. Soc., 83, 3725, 1961, to yield the saturated product 28.8. This material is then converted, using the procedures shown in Scheme 3, into
15 the oxirane 28.9.

Using the above procedures, but employing, in place of the 3-bromophenylalanine derivative 28.5, different bromo compounds 27.2, and/or different alkenyl phosphonates 28.1, the corresponding products 28.4 are obtained.

20 Scheme 29 illustrates the preparation of oxiranes 29.9 in which the phosphonate group is linked by means of an alkylene chain and an oxygen or sulfur atom. In this procedure, a substituted phenylalanine 29.1 is converted into the methyl ester 29.2 by means of a conventional acid-catalyzed esterification reaction. The hydroxy or mercapto substituent is then protected to afford the derivative 29.3. The protection of phenyl hydroxyl and mercapto
25 groups is described respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by
30 T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl, 9-fluorenylmethyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-

methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The protected compound 29.3 is then transformed into the cbz derivative 29.4, using the procedure described above (Scheme 3). The O or S-protecting group is then removed to produce the phenol or thiol 29.5. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978 or by the use of mercuric acetate in trifluoroacetic acid. The resultant phenol or thiophenol 29.5 is then reacted with a dialkyl halo or alkylsulfonyloxyalkyl phosphonate 29.6, to yield the ether or thioether product 29.7. The alkylation reaction is performed at from ambient temperature to about 80°, in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of an organic or inorganic base such as dimethylaminopyridine, triethylamine, potassium carbonate or cesium carbonate. The methyl ester is then hydrolyzed, for example by treatment with lithium hydroxide in aqueous tetrahydrofuran, to afford the carboxylic acid 29.8. The latter compound is then transformed, by means of the reactions shown in Scheme 3, into the oxirane 29.9.

For example, as illustrated in Scheme 29, Example 1, 4-mercaptophenylalanine 29.10, prepared as described in J. Amer. Chem. Soc., 1997, 119, 7173, is reacted with methanol at reflux temperature in the presence of p-toluenesulfonic acid, to yield the methyl ester 29.11. The thiol substituent is then protected by conversion to the S-adamantyl derivative 29.12, for example by reaction with adamantanol in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978. The amino group in the product 29.12 is then protected by conversion to the cbz derivative 29.13, using the procedure described in Scheme 3. Removal of the S-protecting group, for example by treatment of the thioether 29.13 with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978, then affords the thiophenol 29.14. The latter compound is then reacted in dimethylformamide solution with a dialkyl bromoalkylphosphonate, for example a dialkyl bromoethylphosphonate 29.15, (Aldrich) in the presence of a base such as cesium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the thioether 29.16. The methyl

ester is then hydrolyzed as described above, and the resultant carboxylic acid **29.17** is transformed, by means of the reactions shown in Scheme 3, into the oxirane **29.18**.

As a further example of the method of Scheme 29, as shown in Example 2, 3-

hydroxyphenylalanine **29.19** (Fluka) is converted into the methyl ester **29.20**, and the phenolic

5 hydroxyl group is then protected by reaction with one molar equivalent of tert-butylchlorodimethylsilane and imidazole in dimethylformamide, as described in J. Amer. Chem. Soc., 94, 6190, 1972, to produce the silyl ether **29.21**. Conversion to the cbz derivative

29.22, as described above, followed by desilylation, using tetrabutylammonium fluoride in

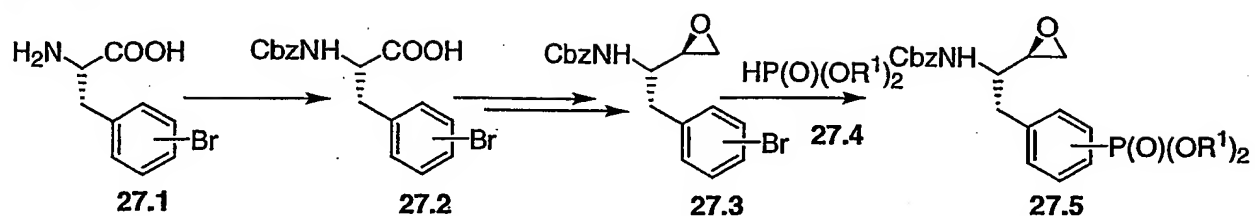
tetrahydrofuran, as described in J. Amer. Chem. Soc., 94, 6190, 1972, then affords the phenol

10 **29.23**. The phenolic hydroxyl group is then reacted in dimethylformamide solution with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate, **29.24**, prepared as described in Tet. Lett., 1986, 27, 1477, and a base such as triethylamine, to afford the ether **29.25**. The methyl ester is then hydrolyzed, as described above, and the resultant carboxylic acid **29.26** is then transformed, by means of the series of reactions shown in Scheme 3, into the oxirane **29.27**.

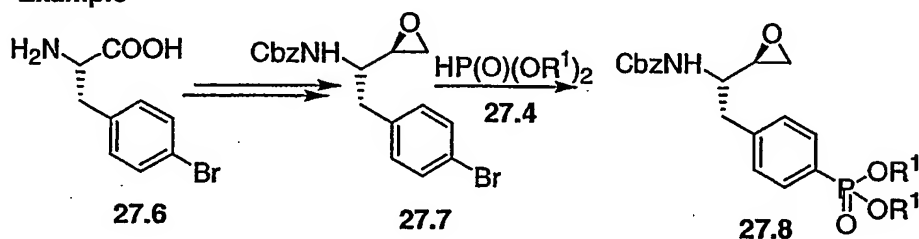
15 Using the above procedures, but employing, in place of the bromoethyl phosphonate **29.15**, or the trifluoromethanesulfonyloxymethyl phosphonate **29.24**, different bromoalkyl or trifluoromethanesulfonyloxyalkyl phosphonates **29.6**, and/or different phenylalanine derivatives **29.1**, the corresponding products **29.9** are obtained.

Scheme 27

Method

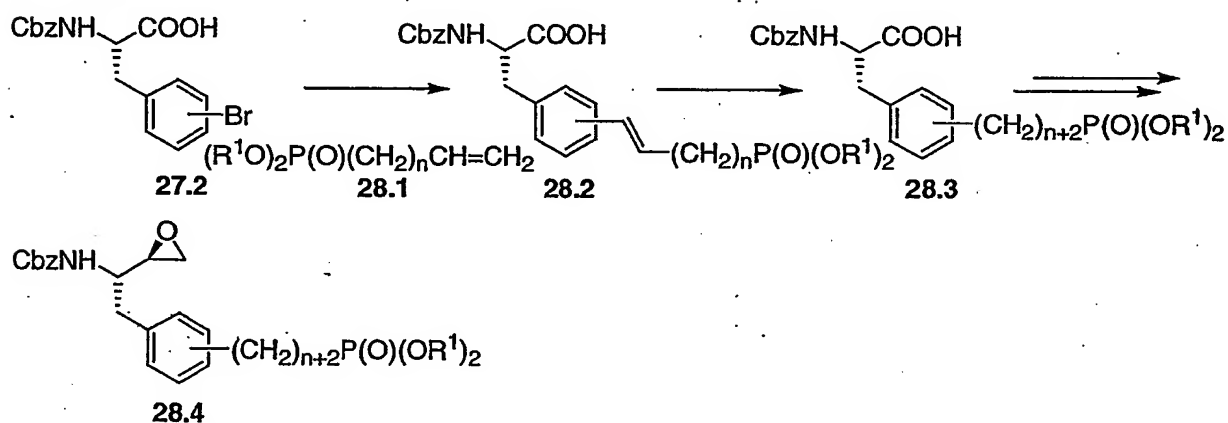


Example

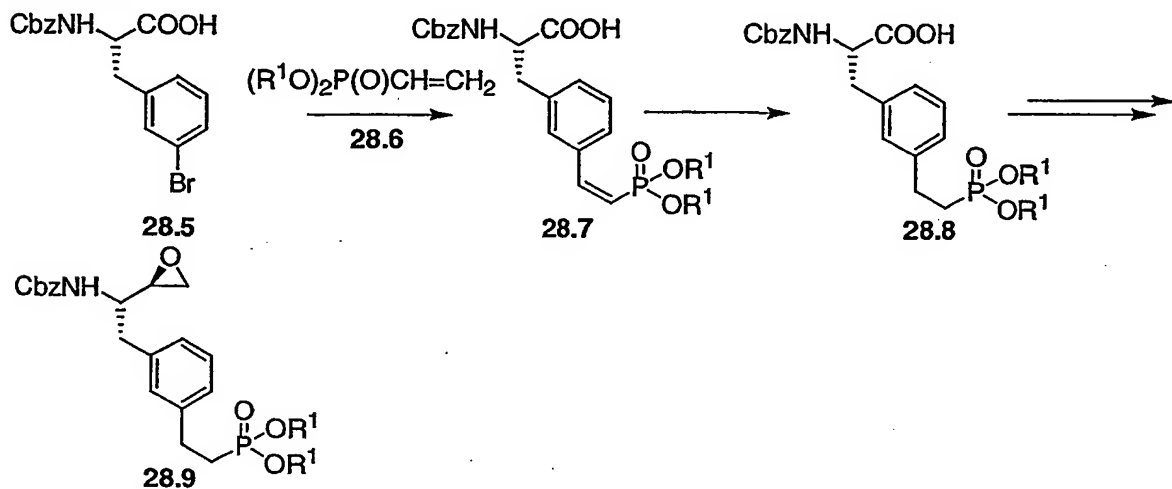


Scheme 28

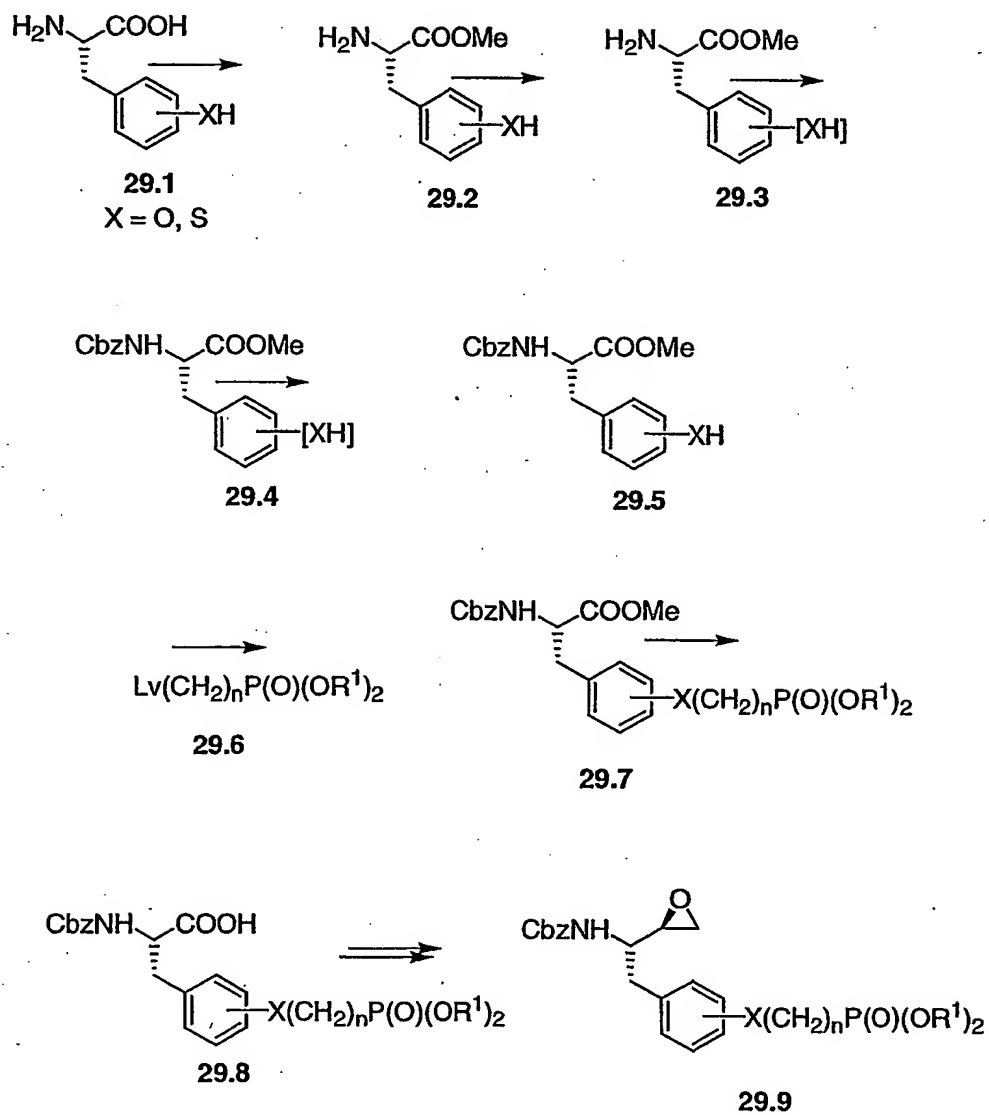
Method



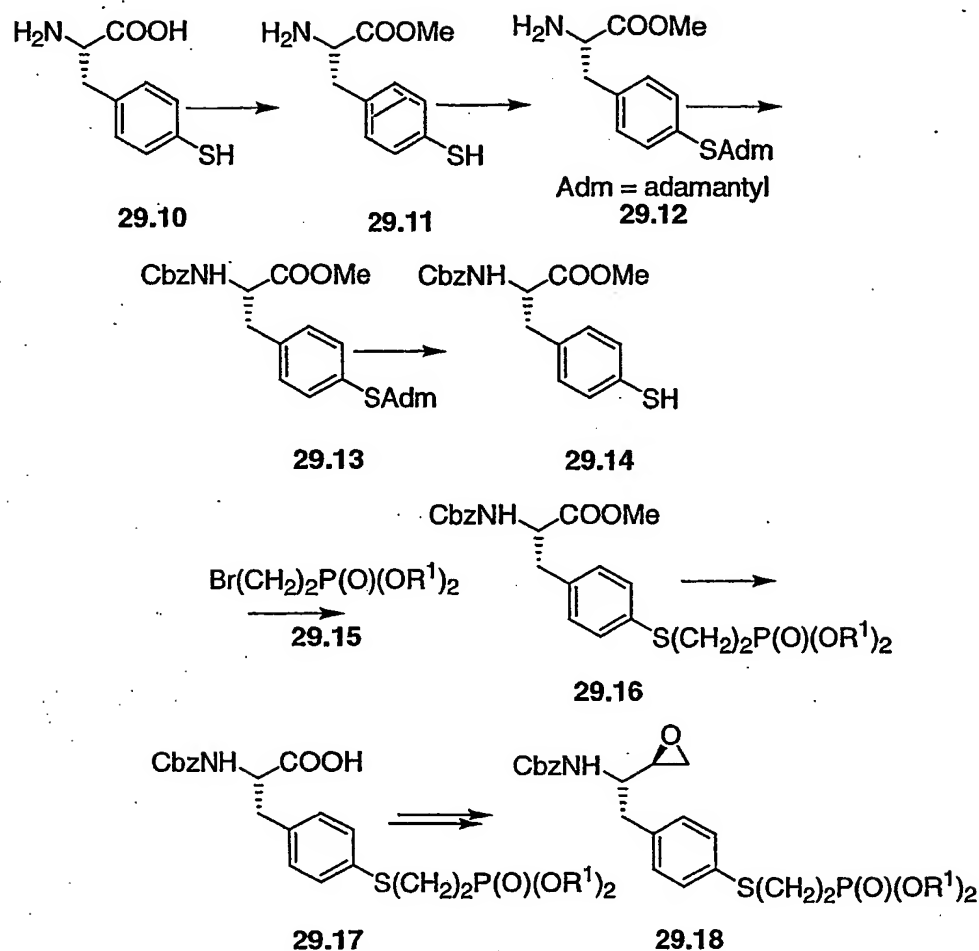
Example



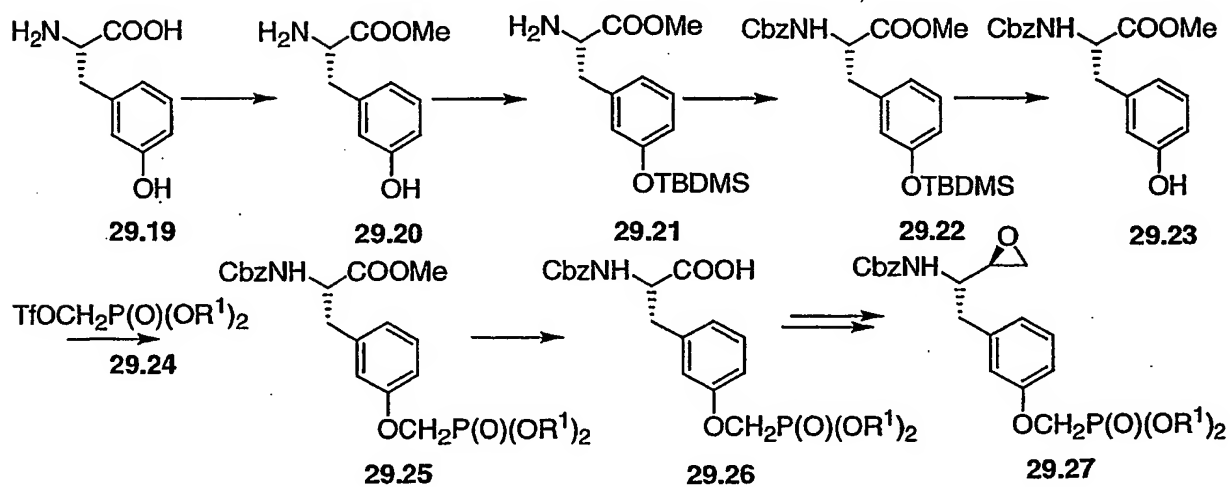
Scheme 29



Example 1



Example 2



Preparation of the phosphonate-containing thiophenol derivatives 10.1.

Schemes 30 - 39 describe the preparation of phosphonate-containing thiophenol derivatives 10.1 which are employed as described above (Schemes 10 and 11) in the preparation of the phosphonate ester intermediates 2.

Scheme 30 depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol 30.1 is protected, as described above (Scheme 29) to afford the protected product 30.2. The product is then coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 30.3. The preparation of arylphosphonates by the coupling of aryl halides with dialkyl phosphites is described above, (Scheme 29). The thiol protecting group is then removed, as described above, to afford the thiol 30.4.

For example, 3-bromothiophenol 30.5 is converted into the 9-fluorenylmethyl (Fm) derivative 30.6 by reaction with 9-fluorenylmethyl chloride and diisopropylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite 30.3, as described for the preparation of the phosphonate 27.8 (Scheme 27), to afford the phosphonate ester 30.7. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol 30.8.

Using the above procedures, but employing, in place of 3-bromothiophenol 30.5, different thiophenols 30.1, and/or different dialkyl phosphites 30.3, the corresponding products 30.4 are obtained.

Scheme 31 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol 31.2 is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative 31.3. The latter compound is reacted with a halodialkyl phosphite 31.4 to afford the product 31.5; deprotection then affords the thiophenol 31.6.

For example, 4-bromothiophenol 31.7 is converted into the S-triphenylmethyl (trityl) derivative 31.8, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **31.9** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorodialkyl phosphite **31.10** to afford the phosphonate **31.11**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **31.12**.
5 Using the above procedures, but employing, in place of the bromo compound **31.7**, different halo compounds **31.2**, and/or different halo dialkyl phosphites **31.4**, there are obtained the corresponding thiols **31.6**.

10 Scheme 32 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol is subjected to free-radical bromination to afford a bromomethyl product **32.1**. This compound is reacted with a sodium dialkyl phosphite **32.2** or a trialkyl phosphite, to give the displacement or rearrangement product **32.3**, which upon
15 deprotection affords the thiophenol **32.4**.

For example, 2-methylthiophenol **32.5** is protected by conversion to the benzoyl derivative **32.6**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **32.7**. This material is reacted with a sodium dialkyl
20 phosphite **32.2**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **32.8**. Alternatively, the bromomethyl compound **32.7** can be converted into the phosphonate **32.8** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **32.7** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100° to produce the phosphonate **32.8**. Deprotection of the
25 phosphonate **32.8**, for example by treatment with aqueous ammonia, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiol **32.9**.

Using the above procedures, but employing, in place of the bromomethyl compound **32.7**, different bromomethyl compounds **32.1**, there are obtained the corresponding thiols **32.4**.

30 Scheme 33 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **33.1** is reacted with a dialkyl hydroxyalkylphosphonate **33.2** under

the conditions of the Mitsunobu reaction, for example as described in *Org. React.*, 1992, 42, 335, to afford the coupled product 33.3. Deprotection then yields the O- or S-linked products 33.4.

- For example, the substrate 3-hydroxythiophenol, 33.5, is converted into the monotrityl ether 33.6, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate 33.7 in benzene, as described in *Synthesis*, 4, 327, 1998, to afford the ether compound 33.8. Removal of the trityl protecting group, as described above, then affords the thiophenol 33.9.
- Using the above procedures, but employing, in place of the phenol 33.5, different phenols or thiophenols 33.1, and different dialkylphosphonates 33.2 there are obtained the corresponding thiols 33.4.

- Scheme 34 illustrates the preparation of thiophenols 34.4 bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol 34.1 is reacted with an activated ester, for example the trifluoromethanesulfonate 34.2, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product 34.3. Deprotection then affords the thiol 34.4.

- For example, 4-methylaminothiophenol 34.5 is reacted with one equivalent of acetyl chloride, as described in *Protective Groups in Organic Synthesis*, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the product 34.6. This material is then reacted with, for example, a dialkyl trifluoromethanesulfonylmethyl phosphonate 34.7, the preparation of which is described in *Tet. Lett.*, 1986, 27, 1477, to afford the displacement product 34.8. Preferably, equimolar amounts of the phosphonate 34.7 and the amine 34.6 are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product 34.8. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in *J. Amer. Chem. Soc.*, 85, 1337, 1963, then affords the thiophenol 34.9.

- Using the above procedures, but employing, in place of the thioamine 34.5, different phenols, thiophenols or amines 34.1, and/or different phosphonates 34.2, there are obtained the corresponding products 34.4.

Scheme 35 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate 35.2. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol 35.1 is reacted with a dialkyl bromoalkyl phosphonate 35.2 to afford the product 35.3. Deprotection then affords the free thiophenol 35.4.

For example, 3-hydroxythiophenol 35.5 is converted into the S-trityl compound 35.6, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate 35.7, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°, to yield the ether product 35.8. Deprotection, as described above, then affords the thiol 35.9.

Using the above procedures, but employing, in place of the phenol 35.5, different phenols, thiophenols or amines 35.1, and/or different phosphonates 35.2, there are obtained the corresponding products 35.4.

Scheme 36 depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 36.2 is coupled with an aromatic bromo compound 36.1. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate 36.4, or the saturated analog 36.6.

For example, 3-bromothiophenol is converted into the S-Fm derivative 36.7, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate 36.8, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a

palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product 36.9. Deprotection, as described above, then affords the
5 thiol 36.10. Optionally, the initially formed unsaturated phosphonate 36.9 is subjected to reduction, for example using diimide, as described above, to yield the saturated product 36.11, which upon deprotection affords the thiol 36.12.

Using the above procedures, but employing, in place of the bromo compound 36.7, different bromo compounds 36.1, and/or different phosphonates 36.2, there are obtained the
10 corresponding products 36.4 and 36.6

Scheme 37 illustrates the preparation of an aryl-linked phosphonate ester 37.4 by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock,
15 VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid 37.1 is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product 37.3 which is deprotected to yield the thiol 37.4.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane,
20 in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate 37.5. This material is reacted with diethyl 4-bromophenylphosphonate 37.6, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the
25 presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product 37.7. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol 37.8.

Using the above procedures, but employing, in place of the boronate 37.5, different boronates 37.1, and/or different phosphonates 37.2, there are obtained the corresponding products 37.4.

30 Scheme 38 depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol

38.1 is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate 38.2, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product 38.3 is then deprotected to afford the thiol 38.4. For example, 1,4-

5 dimercaptobenzene is converted into the monobenzoyl ester 38.5 by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol 38.5 is then reacted with, for example diethyl 4-(bromomethyl)phenylphosphonate, 38.6, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The thioether product 38.7 thus obtained is deprotected, as described
10 above, to afford the thiol 38.8.

Using the above procedures, but employing, in place of the thiophenol 38.5, different phenols, thiophenols or amines 38.1, and/or different phosphonates 38.2, there are obtained the corresponding products 38.4.

15

Scheme 39 illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol 39.1, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is $CH=CH$) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted
20 with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate 39.2, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester 39.3. Deprotection, as described above, then affords the thiol 39.4. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the
25 corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in
30 J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived

organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p. 707.

For example, 2,3-dihydro-1H-indole-5-thiol, 39.5, the preparation of which is described in EP 209751, is converted into the benzoyl ester 39.6, as described above, and the ester is then

5 reacted with the trifluoromethanesulfonate 39.7, using the conditions described above for the preparation of the phosphonate 34.8, (Scheme 34), to yield the phosphonate 39.8.

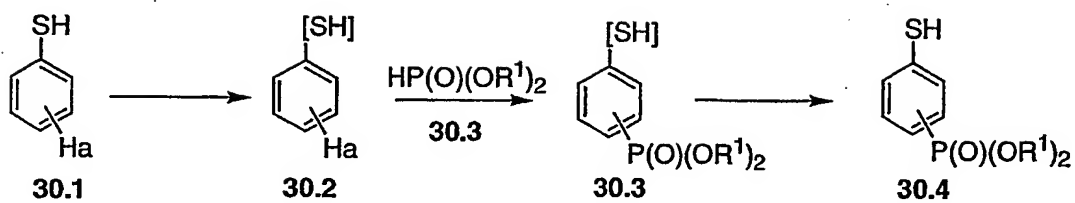
Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol 39.9.

Using the above procedures, but employing, in place of the thiol 39.5, different thiols 39.1,

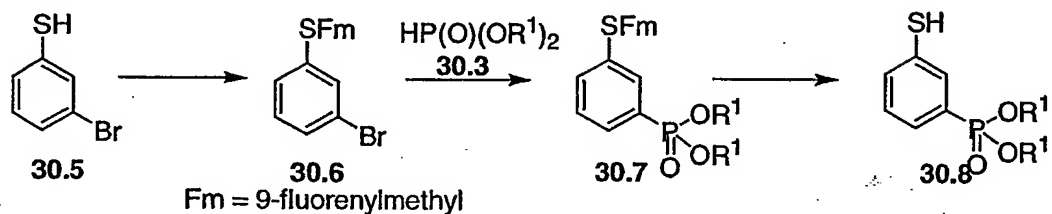
10 and/or different triflates 39.2, there are obtained the corresponding products 39.4.

Scheme 30

Method

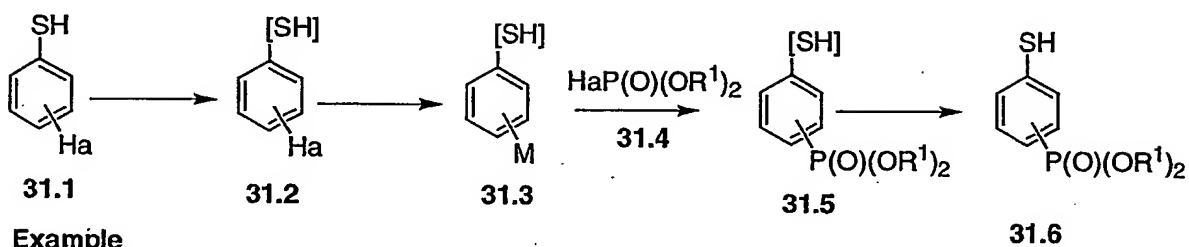


Example

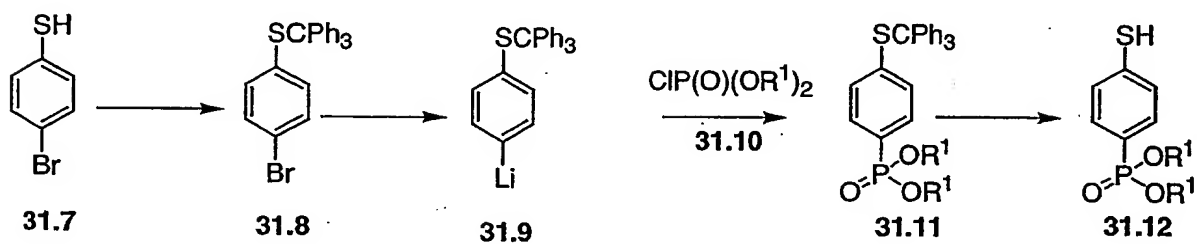


Scheme 31

Method

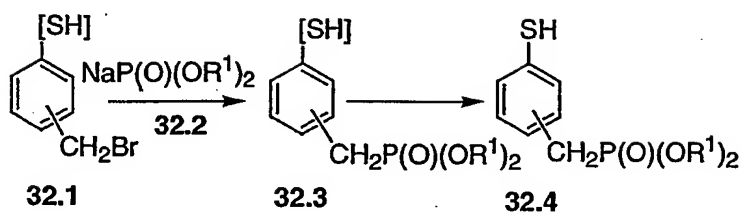


Example

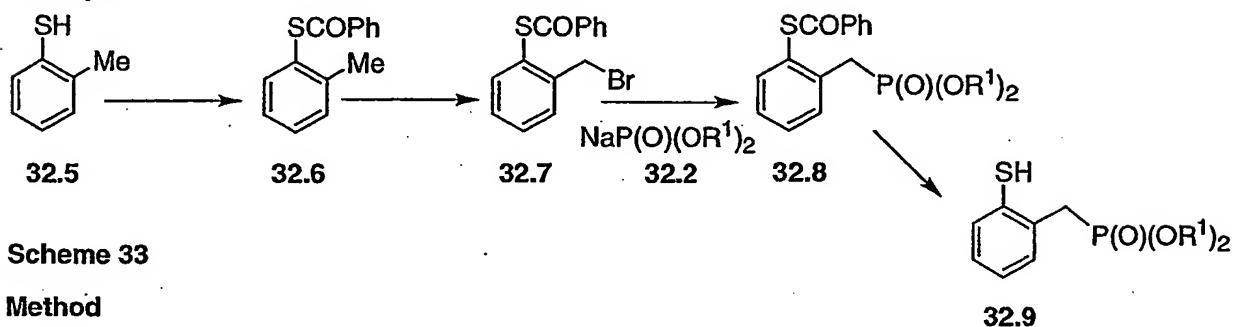


Scheme 32

Method

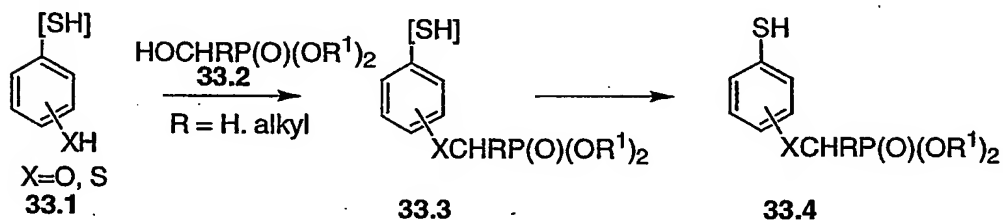


Example

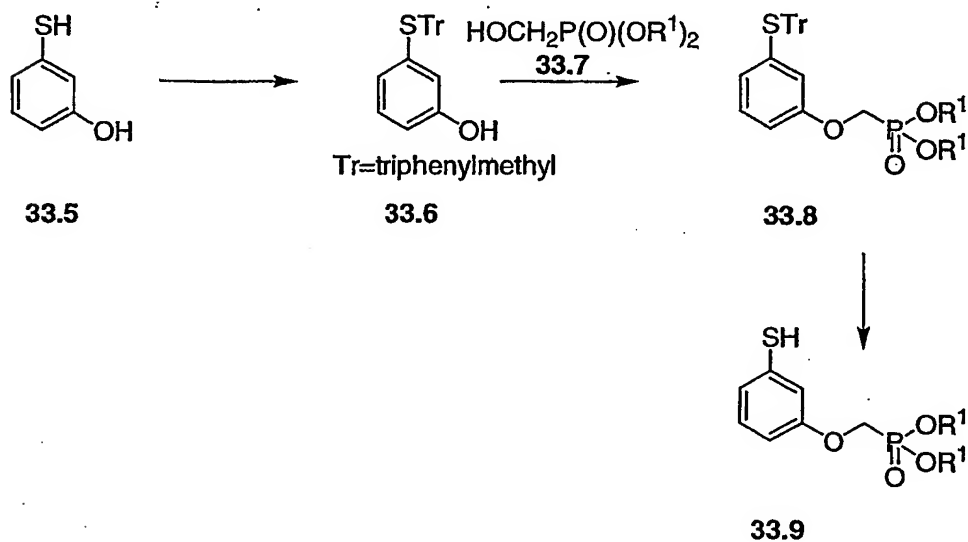


Scheme 33

Method

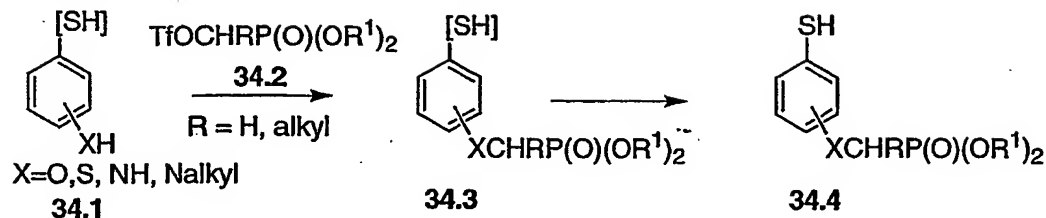


Example

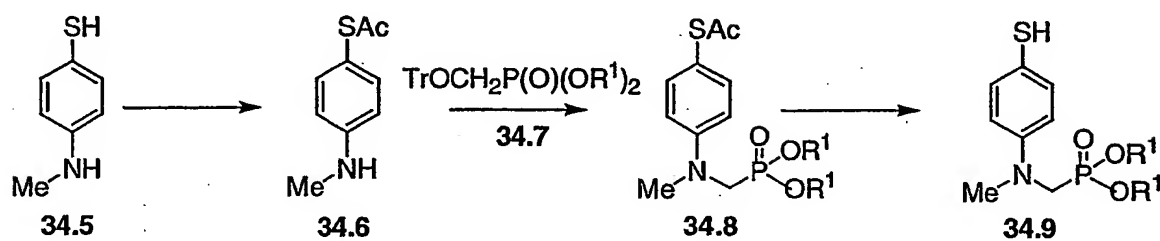


Scheme 34

Method

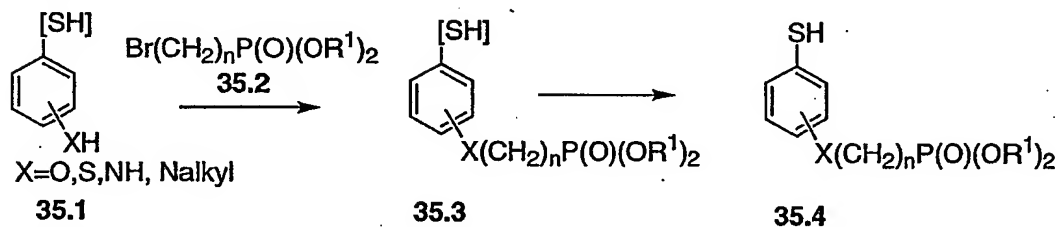


Example

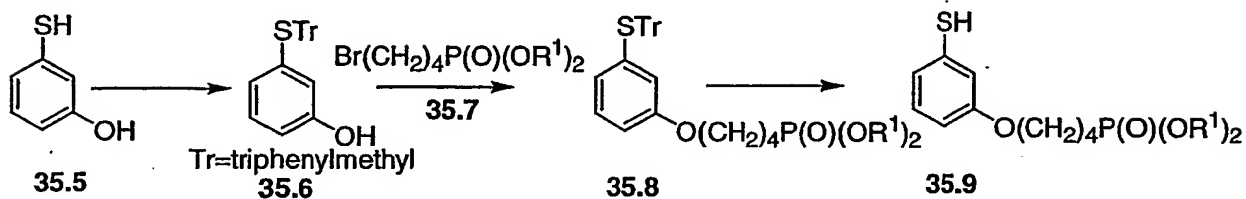


Scheme 35

Method

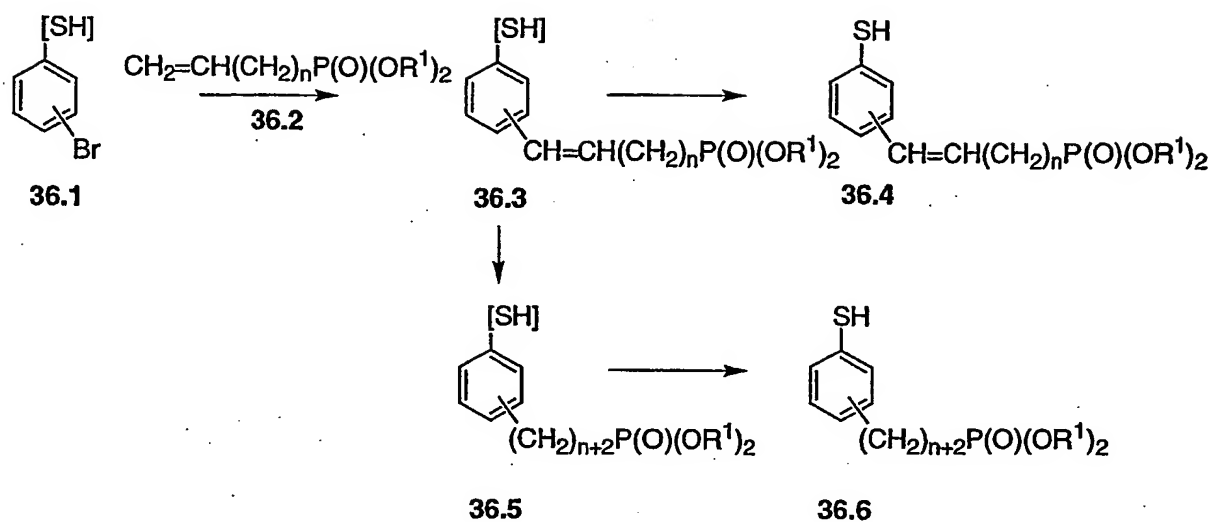


Example

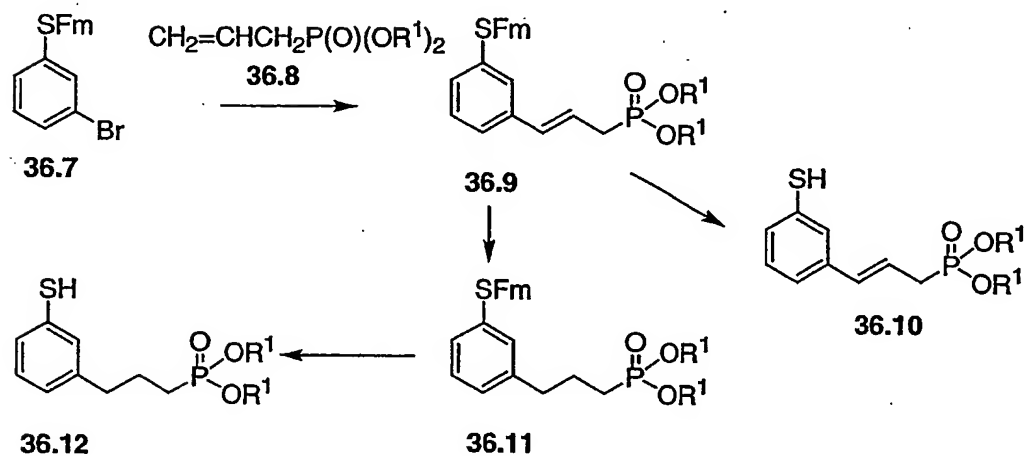


Scheme 36

Method

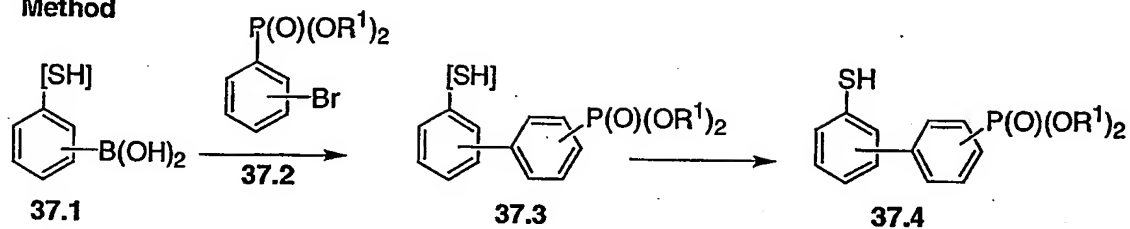


Example

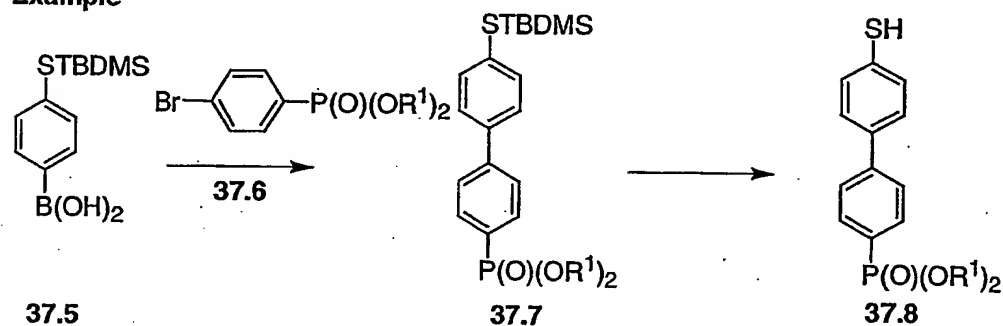


Scheme 37

Method

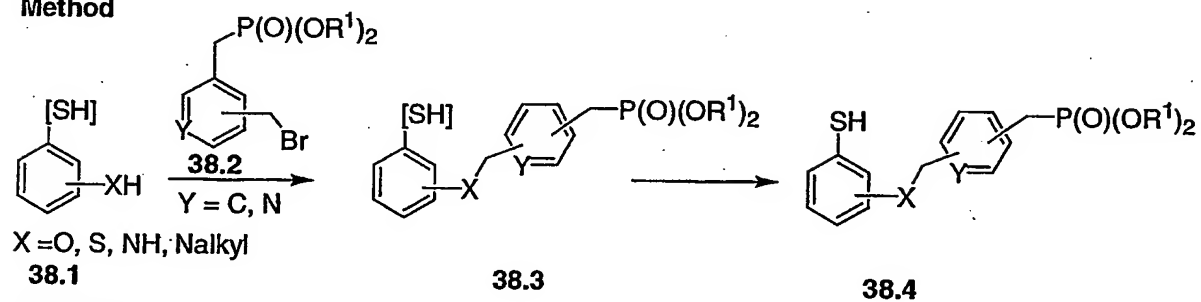


Example

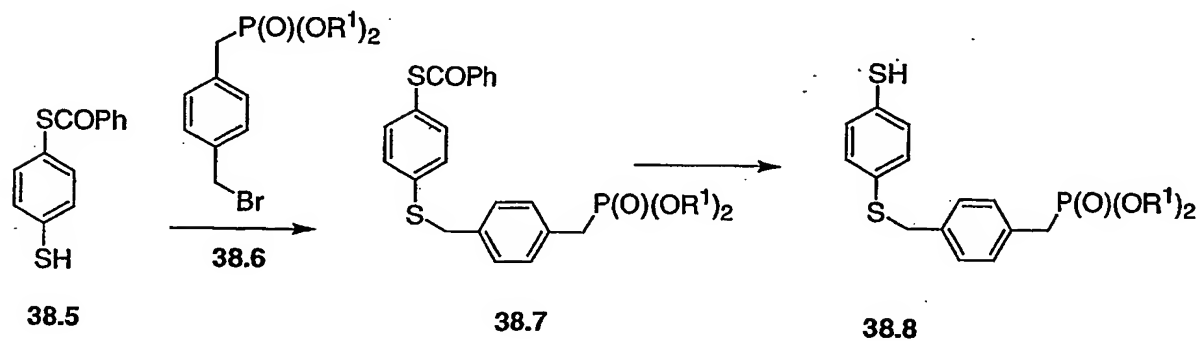


Scheme 38

Method

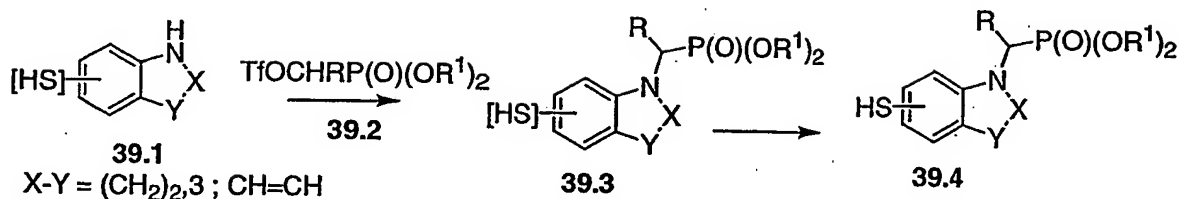


Example

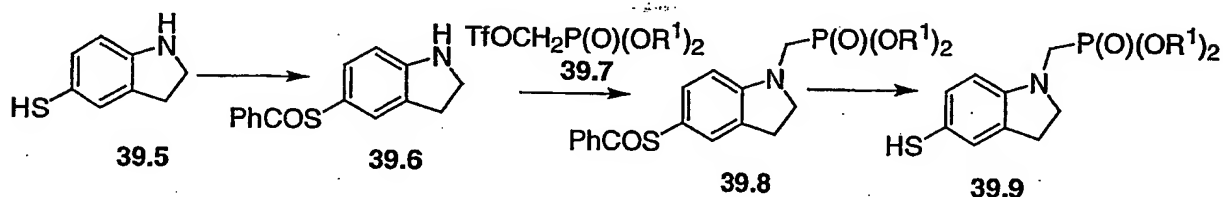


Scheme 39

Method



Example



Preparation of the phenylpyridylphosphonate aldehydes 4.9.

5

Schemes 40 and 41 illustrate methods for the preparation of 4-(2-pyridyl)benzaldehydes 4.9 incorporating phosphonate groups, which are employed in the preparation of the phosphonate ester intermediates 3a.

Scheme 40 illustrates the preparation of benzaldehydes substituted at the 4 position with a bromo-substituted 2-pyridine group, and the conversion of the bromo substituent into various phosphonate substituents, linked to the pyridine ring either directly, or by means of a saturated or unsaturated alkylene chain, or by a heteroatom and an alkylene chain.

In this procedure, a 4-formylphenylboronate 40.1 (Lancaster Synthesis) is coupled with a dibromopyridine 40.2 to afford the bromopyridyl benzaldehyde product 40.3. Equimolar amounts of the reactants are combined in the presence of a palladium catalyst, as described above (Scheme 4). The bromopyridine product 40.3 is then reacted with a dialkyl phosphite 40.4, in the presence of a palladium catalyst, as described above (Scheme 27) to afford the pyridylphosphonate ester 40.5. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.

Alternatively, the bromopyridine compound 40.3 is coupled, in the presence of a palladium catalyst, with a dialkyl alkenylphosphonate 40.6, to yield the alkenyl phosphonate 40.9, using

the procedures described above, (Scheme 28). The olefinic bond present in the product is then reduced to afford the saturated analog 40.8. The reduction reaction is performed catalytically, for example by the use of palladium on carbon and hydrogen or a hydrogen donor, or chemically, for example by employing diimide, generated by treatment of disodium azodicarboxylate with acetic acid, as described in J. Am. Chem. Soc., 83, 3725, 1961.

Alternatively, the bromopyridine compound 40.3, in which the bromo substituent is in either the 4 or 6 position, is transformed, by reaction with a dialkyl hydroxy, mercapto or aminoalkyl phosphonate 40.7, into the ether, thioether or amine product 40.10. The preparation of pyridine ethers, thioethers and amines by means of displacement reactions of 2- or 4-bromopyridines by alcohols, thiols and amines is described, for example, in Heterocyclic Compounds, Volume 3, R. A. Abramovitch, ed., Wiley, 1975, p. 597, 191, and 41 respectively. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide at ca 100° in the presence of a base such as potassium carbonate, to effect the displacement reaction.

Scheme 40, Example 1, illustrates the coupling reaction of 4-formylphenylboronic acid 40.1 with 2,5-dibromopyridine 40.11, using the procedure described above, to afford 4-(5-bromo-2-pyridyl)benzaldehyde 40.12. This compound is then coupled, as described above, with a dialkyl phosphite 40.4, to afford the pyridyl phosphonate 40.13.

Using the above procedures, but employing, in place of 2,5-dibromopyridine 40.11, different dibromopyridines 40.2, and/or different dialkyl phosphites 40.4, the corresponding products 40.5 are obtained.

Alternatively, as illustrated in Scheme 40, Example 2, the phenylboronic acid 40.1 is coupled, as described above, with 2,4-dibromopyridine 40.14 to afford 4-(4-bromo-2-pyridyl)benzaldehyde 40.15. The product is then reacted with a dialkyl mercaptoethyl phosphonate 40.16, the preparation of which is described in Zh. Obschei. Khim., 1973, 43, 2364, to yield the thioether 40.17. Equimolar amounts of the reactants are combined in dimethylformamide at 80° in the presence of potassium carbonate, to effect the displacement reaction.

Using the above procedures, but employing, in place of the dialkyl mercaptoethyl phosphonate 40.16, different dialkyl hydroxy, mercapto or aminoalkyl phosphonates 40.7, the corresponding products 40.10 are obtained.

Alternatively, as shown in Scheme 40, Example 3, 4-(5-bromo-2-pyridyl)benzaldehyde 40.12 is coupled with a dialkyl vinyl phosphonate 40.18, in the presence of a palladium catalyst, as described above, to afford the unsaturated phosphonate 40.19. Optionally, the product can be reduced to the saturated analog 40.20, for example by the use of diimide, as described above.

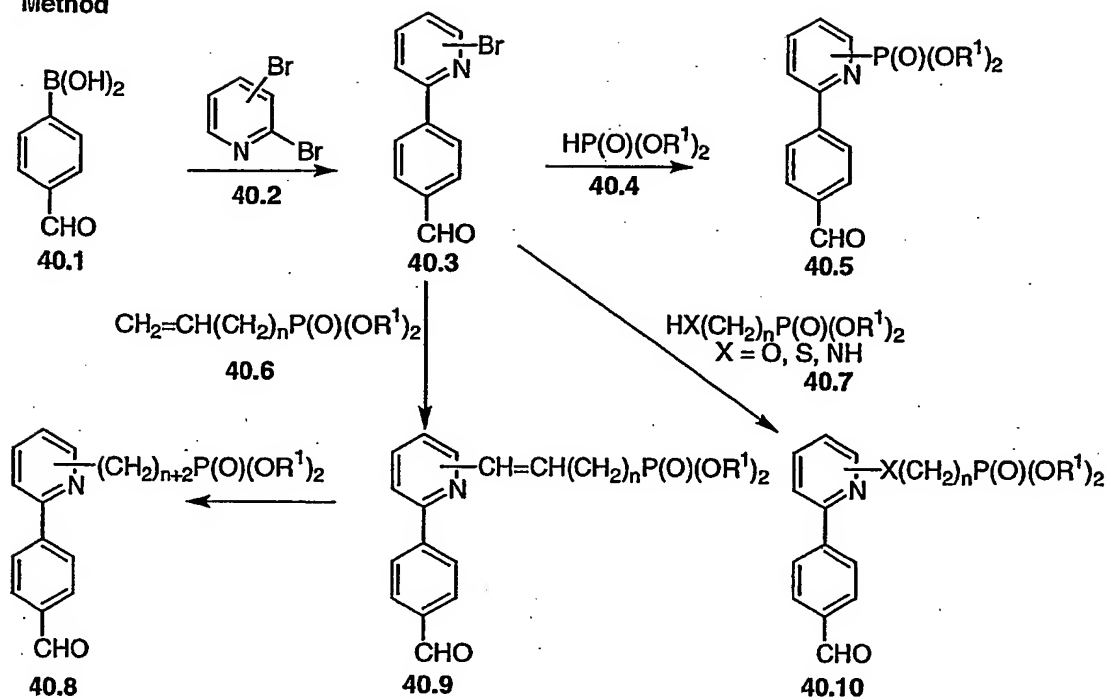
5 Using the above procedures, but employing, in place of the bromoaldehyde 40.12, different bromoaldehydes 40.3, and/or, in place of the dialkyl vinylphosphonate 40.18, different dialkyl alkenylphosphonates 40.6, the corresponding products 40.8 and 40.9 are obtained.

Scheme 41 illustrates the preparation of 4-(2-pyridyl)benzaldehydes incorporating
10 phosphonate group linked by means of a alkylene chain incorporating a nitrogen atom. In this procedure, a formyl-substituted 2-bromopyridine 41.2 is coupled, as described above, (Scheme 40) with a 4-(hydroxymethyl)phenylboronic acid 41.1. prepared as described in Macromolecules, 2001, 34, 3130, to afford the 4-(2-pyridyl)benzyl alcohol 41.3. The product is then reacted with a dialkyl aminoalkyl phosphonate 41.4, under reductive amination
15 conditions. The preparation of amines by means of a reductive amination of an aldehyde is described above (Scheme 24). The resultant benzyl alcohol 41.5 is then oxidized to yield the corresponding benzaldehyde 41.6. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate,
20 silver carbonate, or dimethyl sulfoxide/acetic anhydride. The reaction is conducted in an inert aprotic solvent such as dichloromethane or toluene. Preferably, the alcohol 41.5 is oxidized to the aldehyde 41.6 by reaction with pyridinium chlorochromate in dichloromethane.

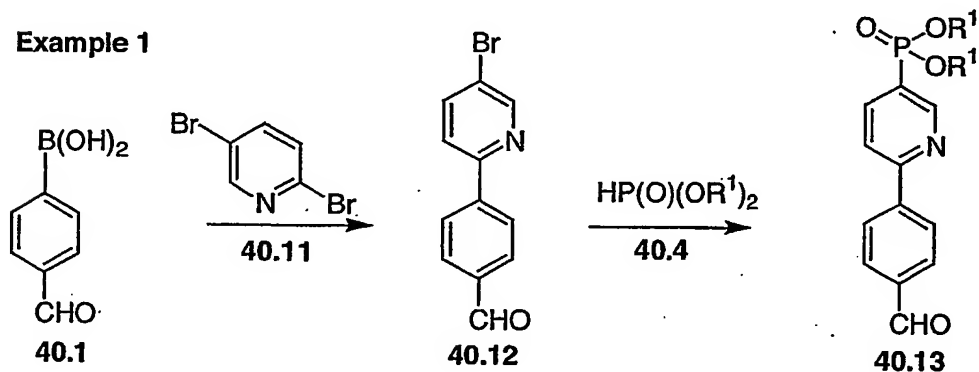
For example, the phenylboronic acid 41.1 is coupled with 2-bromopyridine-4-carboxaldehyde 41.7, the preparation of which is described in Tet. Lett. 2001, 42, 6815, to afford 4-(4-formyl-
25 2-pyridyl)benzyl alcohol 41.8. The aldehyde is then reductively aminated by reaction with a dialkyl aminoethylphosphonate 41.9, the preparation of which is described in J. Org. Chem., 2000, 65, 676, and a reducing agent, to afford the amine product 41.10. The latter compound is then oxidized, for example by treatment with pyridinium chlorochromate, to afford the aldehyde phosphonate 41.11.

30 Using the above procedures, but employing, in place of the bromopyridine aldehyde 41.7, different aldehydes 41.2, and/or different dialkyl aminoalkyl phosphonates 41.4, the corresponding products 41.6 are obtained.

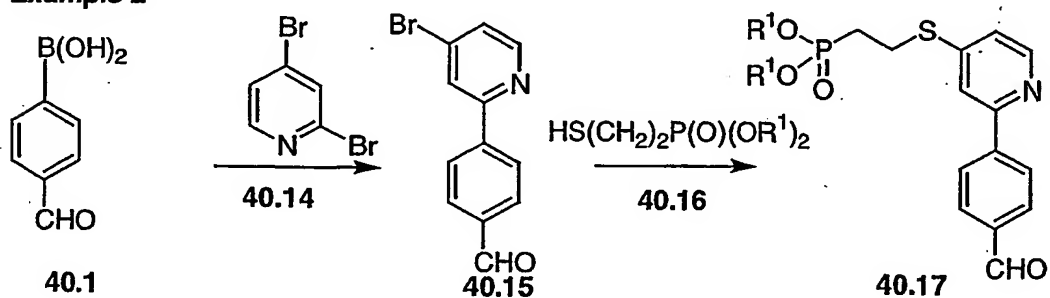
Scheme 40
Method

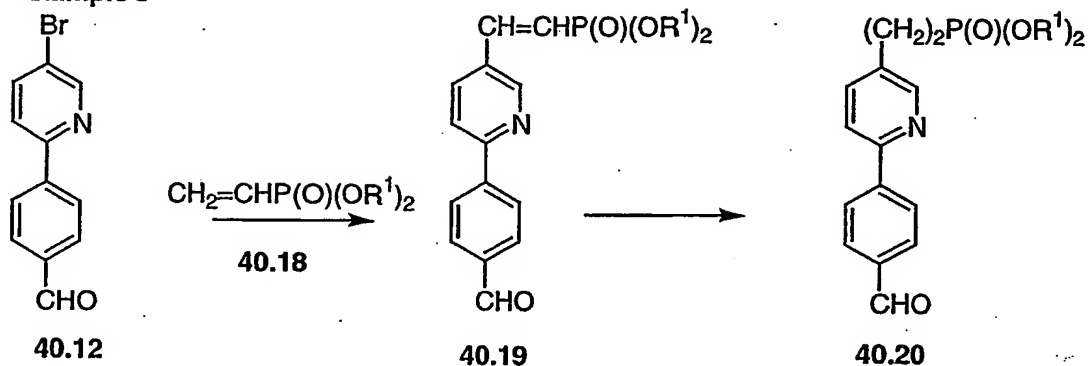
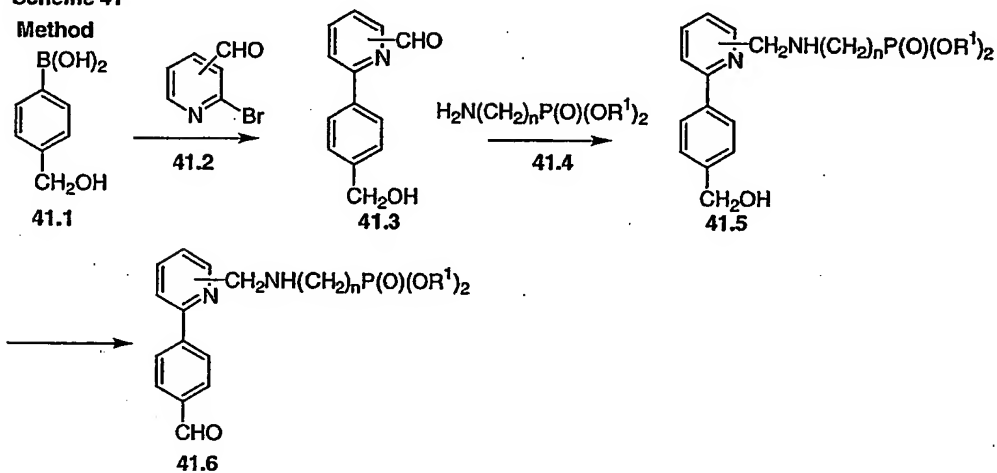
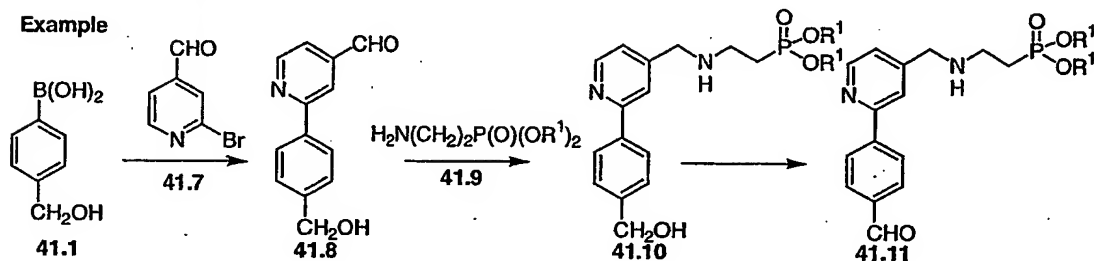


Example 1



Example 2



Example 3**Scheme 41****Method****Example****5 Preparation of the biphenyl phosphonate aldehydes 4.12.**

Schemes 42 - 44 illustrate methods for the preparation of the biphenylphosphonate aldehydes 4.12 which are employed in the synthesis of the phosphonate esters 3b.

Scheme 42 depicts the preparation of biphenyl aldehyde phosphonates in which the phosphonate moiety is attached to the phenyl ring either directly, or by means of a saturated or unsaturated alkylene chain. In this procedure, 4-formylbenzeneboronic acid 42.1 and a

dibromobenzene 42.2 are coupled in the presence of a palladium catalyst, as described above, to produce the bromobiphenyl aldehyde 42.3. The aldehyde is then coupled, as described above, with a dialkyl phosphite 42.4, to afford the phosphonate ester 42.5. Alternatively, the bromoaldehyde 42.3 is coupled with a dialkyl alkenylphosphonate 42.6, using the procedures described above, to afford the alkenyl phosphonate 42.8. Optionally, the latter compound is reduced to yield the saturated analog 42.7.

For example, as shown in Scheme 42, Example 1, 4-formylbenzeneboronic acid 42.1 is coupled with 1,3-dibromobenzene 42.9 to give 3'-bromo-4-formylbiphenyl 42.10. The product is then coupled, as described above, with a dialkyl phosphite 42.4 to give the biphenyl phosphonate ester 42.11.

Using the above procedures, but employing, in place of 1,3-dibromobenzene 42.9, different dibromobenzenes 42.2, and/or different dialkyl phosphites 42.4, the corresponding products 42.5 are obtained.

As a further example of the methods of Scheme 42, as shown in Example 2, 4'-bromobiphenyl-4-aldehyde 42.12 is coupled with a dialkyl propenylphosphonate 42.13 (Aldrich) in the presence of a palladium catalyst, to produce the propenyl phosphonate 42.15. Optionally, the product is reduced, for example by catalytic hydrogenation over a palladium catalyst, to yield the saturated product 42.16.

Using the above procedures, but employing, in place of the 4-bromobiphenyl aldehyde 42.12, different bromobiphenyl aldehydes, and/or different alkenyl phosphonates 42.6, the corresponding products 42.7 and 42.8 are obtained.

Scheme 43 illustrates the preparation of biphenyl phosphonates in which the phosphonate group is attached by means of a single carbon or by a heteroatom O, S or N and an alkylene chain. In this procedure, a bromotoluene 43.2 is coupled with 4-formylbenzeneboronic acid 43.1 to yield the methyl-substituted biphenyl aldehyde 43.3. The product is then subjected to a free radical bromination to produce the bromomethyl compound 43.4. The conversion of aromatic methyl groups into the corresponding benzylic bromide is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 313. The transformation is effected, for example, by the use of bromine, N-bromosuccinimide, carbon tetrabromide or bromotrichloromethane. The reaction is performed in an inert organic solvent such as carbon tetrachloride, ethyl acetate and the like, at reflux temperature, optionally in the

presence of an initiator such as dibenzoyl peroxide. Preferably, the conversion of the methyl compound 43.3 to the bromomethyl product 43.4 is effected by the use of one molar equivalent of N-bromosuccinimide in refluxing carbon tetrachloride. The bromomethyl compound is then reacted with a sodium dialkyl phosphonate 43.5 to afford the phosphonate product 43.6. The displacement reaction is performed in an inert solvent such as tetrahydrofuran, at from ambient temperature to reflux, as described in J. Med. Chem., 1992, 35, 1371.

Alternatively, the bromomethyl compound 43.4 is reacted with a dialkyl hydroxy, mercapto or aminoalkyl phosphonate 43.7 to prepare the corresponding ether, thioether or aminoalkyl phosphonate products 43.8. The reaction is performed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, at from ambient temperature to about 80°, in the presence of an inorganic or organic base. For the preparation of the ethers 43.8 in which X is O, a strong base such as sodium hydride or potassium tert. butoxide is employed. For the preparation of the thioethers or amines 43.8, a base such as cesium carbonate, dimethylaminopyridine or diisopropylethylamine is employed.

Scheme 43, Example 1 depicts the coupling reaction of 4-formylbenzeneboronic acid 43.1 with 3-bromotoluene 43.9 to afford 3'-methylbiphenyl-4-aldehyde 43.10. The product is then reacted with N-bromosuccinimide, as described above, to afford the bromomethyl product 43.11. This material is reacted with a sodium dialkyl phosphonate 43.5 to afford the phosphonate ester 43.12.

Using the above procedures, but employing, in place of 3-bromotoluene 43.9, different bromotoluenes 43.2, the corresponding products 43.6 are obtained.

Scheme 43, Example 2 shows the free-radical bromination of 4'-methylbiphenyl-4-aldehyde to give the 4'-bromomethylbiphenyl-4-aldehyde 43.14. The product is then reacted in acetonitrile solution at 70° with one molar equivalent of a dialkyl aminoethyl phosphonate 43.15, the preparation of which is described in J. Org. Chem., 2000, 65, 676, and cesium carbonate, to yield the amine product 43.16.

Using the above procedures, but employing, in place of the aminoethyl phosphonate 43.15, different hydroxy, mercapto or aminoalkyl phosphonates 43.7, and/or different biphenyl aldehydes 43.3, the corresponding products 43.8 are obtained.

Scheme 44 illustrates the preparation of the biphenyl phosphonates 44.3 in which the phosphonate group is attached by means of a heteroatom and an alkylene chain. In this procedure, a hydroxy, mercapto or amino-substituted biphenyl aldehyde 44.1 is reacted with a dialkyl bromoalkyl phosphonate 44.2 to afford the alkylation product 44.3. The reaction is conducted between equimolar amounts of the reactants in a polar organic solvent such as dimethylformamide and the like, at from ambient temperature to about 80°, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of an inorganic iodide such as potassium iodide.

For example, 3'-hydroxybiphenyl-4-aldehyde 44.4 is reacted with a dialkyl bromoethyl phosphonate 44.5 (Aldrich) and potassium carbonate in dimethylformamide at 80°, to produce the ether 44.6.

Using the above procedures, but employing, in place of 3'-hydroxybiphenyl-4-aldehyde 44.4, different hydroxy, mercapto or aminobiphenyl-4-aldehydes 44.1, and/or different bromoalkyl phosphonates 44.2, the corresponding products 44.3 are obtained.

Preparation of the benzaldehyde phosphonates 4.14.

Schemes 45 - 48 illustrate methods for the preparation of the benzaldehyde phosphonates 4.14 which are employed in the synthesis of the phosphonate esters 3d.

Scheme 45 illustrates the preparation of benzaldehyde phosphonates 45.3 in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde 45.1 is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate 45.2, under reductive amination conditions, as describe above in Scheme 24, to yield the phosphonate product 45.3.

For example, benzene-1,3-dialdehyde 45.4 is reacted with a dialkyl aminopropyl phosphonate 45.5, (Acros) and sodium triacetoxyborohydride, to afford the product 45.6.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde 45.4, different benzene dialdehydes 45.1, and/or different phosphonates 45.2, the corresponding products 45.3 are obtained.

Scheme 46 illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated carbon chain. In this

procedure, a bromobenzaldehyde 46.1 is coupled, under palladium catalysis as described above, with a dialkyl alkenylphosphonate 46.2, to afford the alkenyl phosphonate 46.3. Optionally, the product can be reduced, as described above, to afford the saturated phosphonate ester 46.4. Alternatively, the bromobenzaldehyde can be coupled, as described
5 above, with a dialkyl phosphite 46.5 to afford the formylphenylphosphonate 46.6.

For example, as shown in Example 1, 3-bromobenzaldehyde 46.7 is coupled with a dialkyl propenylphosphonate 46.8 to afford the propenyl product 46.9. Optionally, the product is reduced to yield the propyl phosphonate 46.10.

Using the above procedures, but employing, in place of 3-bromobenzaldehyde 46.7, different
10 bromobenzaldehydes 46.1, and/or different alkenyl phosphonates 46.2, the corresponding products 46.3 and 46.4 are obtained.

Alternatively, as shown in Example 2, 4-bromobenzaldehyde 46.11 is coupled with a dialkyl phosphite 46.5 to afford the 4-formylphenyl phosphonate product 46.12.

Using the above procedures, but employing, in place of 4-bromobenzaldehyde 46.11, different
15 bromobenzaldehydes 46.1, the corresponding products 46.6 are obtained.

Scheme 47 illustrates the preparation of formylphenyl phosphonates in which the phosphonate moiety is attached by means of alkylene chains incorporating two heteroatoms O, S or N. In this procedure, a formyl phenoxy, phenylthio or phenylamino alkanol, alkanethiol or
20 alkylamine 47.1 is reacted with an equimolar amount of a dialkyl haloalkyl phosphonate 47.2, to afford the phenoxy, phenylthio or phenylamino phosphonate product 47.3. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile 47.1. In cases in which Y is O, a strong base such as sodium hydride or lithium
25 hexamethyldisilazide is employed. In cases in which Y is O or N, a base such as cesium carbonate or dimethylaminopyridine is employed.

For example, 2-(4-formylphenylthio)ethanol 47.4, prepared as described in Macromolecules, 1991, 24, 1710, is reacted in acetonitrile at 60° with one molar equivalent of a dialkyl iodomethyl phosphonate 47.5, (Lancaster) to give the ether product 47.6.

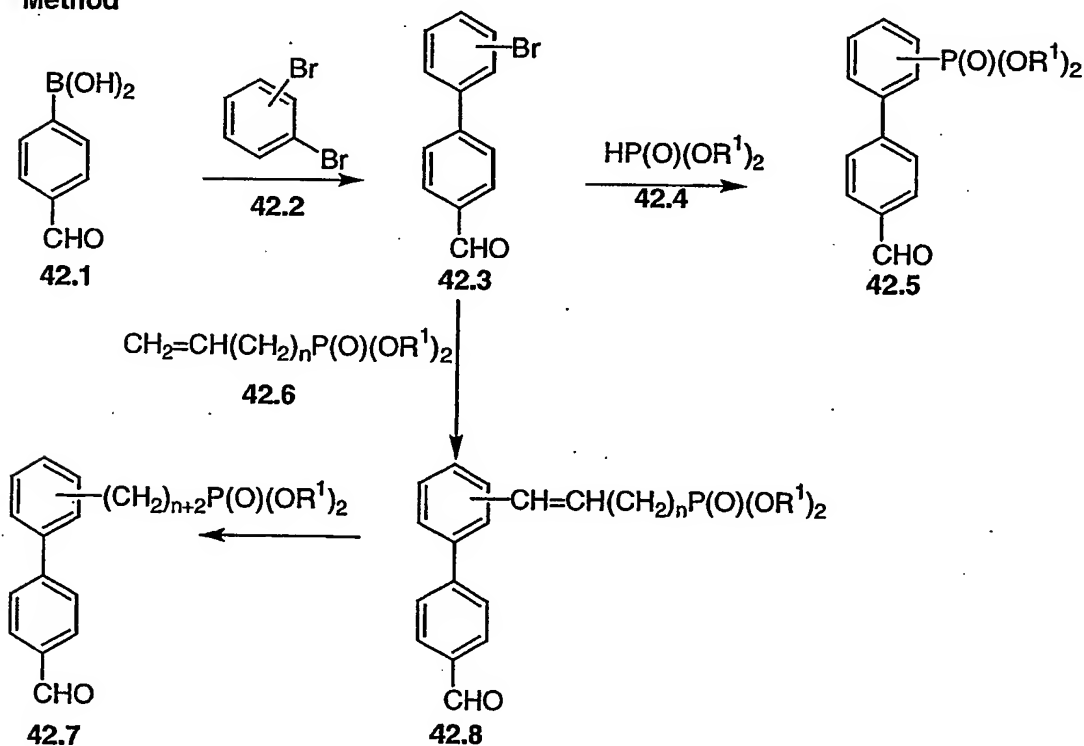
Using the above procedures, but employing, in place of the carbinol 47.4, different carbinols,
30 thiols or amines 47.1, and/or different haloalkyl phosphonates 47.2, the corresponding products 47.3 are obtained.

Scheme 48 illustrates the preparation of formylphenyl phosphonates in which the phosphonate group is linked to the benzene ring by means of an aromatic or heteroaromatic ring. In this procedure, 4-formylbenzeneboronic acid **43.1** is coupled, as described previously, with one molar equivalent of a dibromoarene, **48.1**, in which the group Ar is an aromatic or heteroaromatic group. The product **48.2** is then coupled, as described above (Scheme 46) with a dialkyl phosphite **40.4** to afford the phosphonate **48.3**.

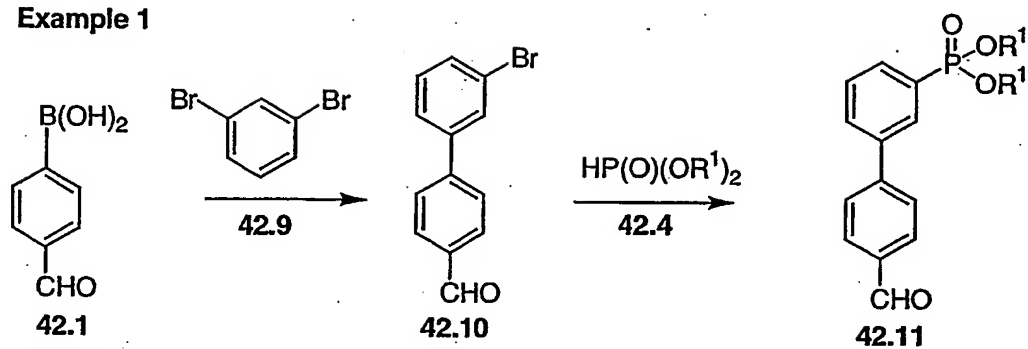
For example, 4-formylbenzeneboronic acid **43.1** is coupled with 2,5-dibromothiophene **48.4** to yield the phenylthiophene product **48.5**. This compound is then coupled with the dialkyl phosphite **40.4** to afford the thienyl phosphonate **48.6**.

Using the above procedures, but employing, in place of dibromothiophene **48.4**, different dibromoarenes **48.1**, the corresponding products **48.3** are obtained.

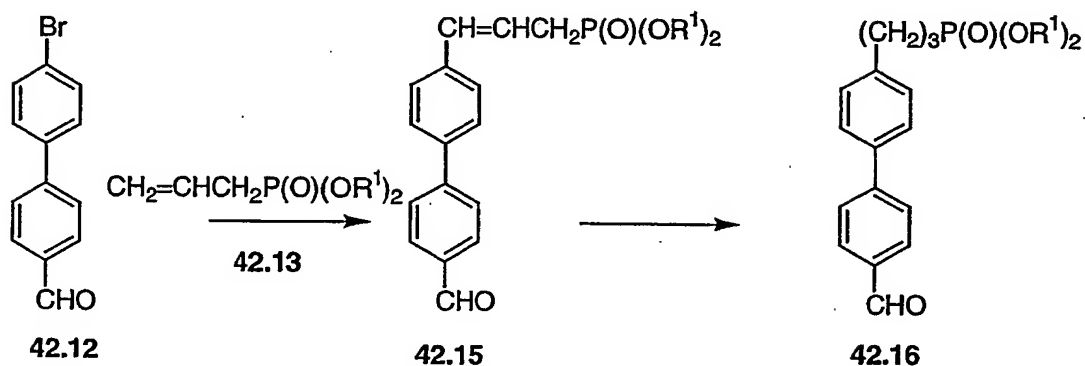
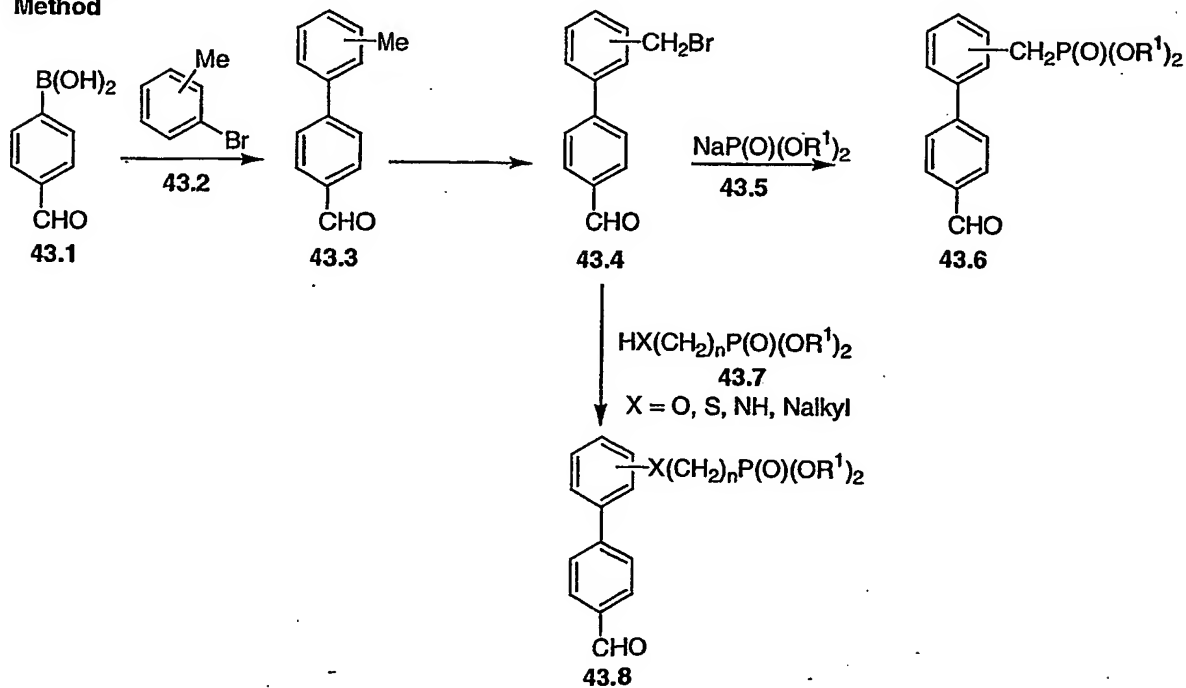
Scheme 42
Method



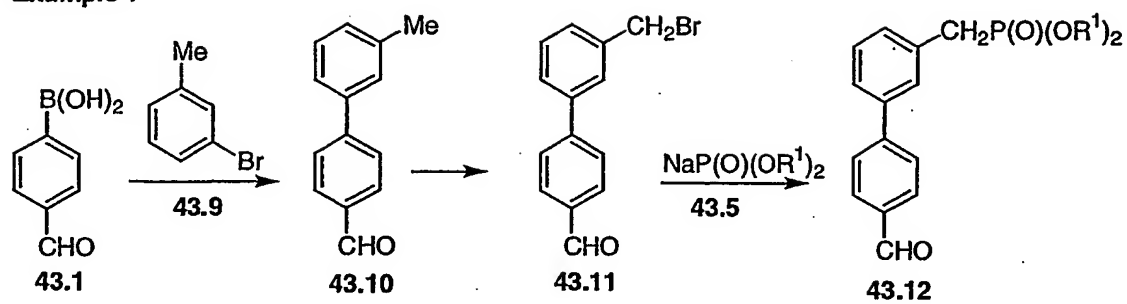
Example 1



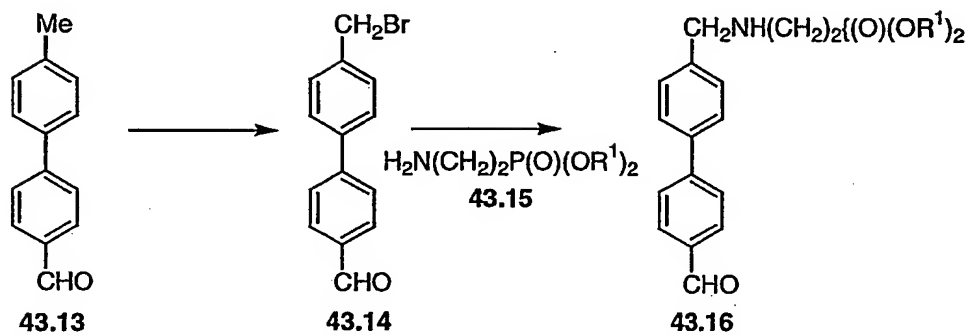
Example 2

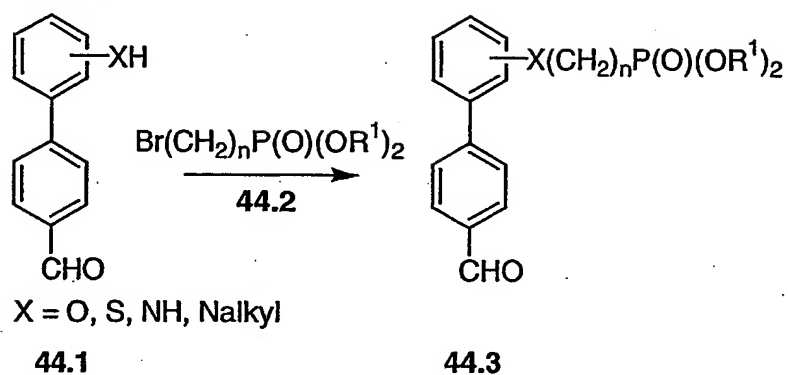
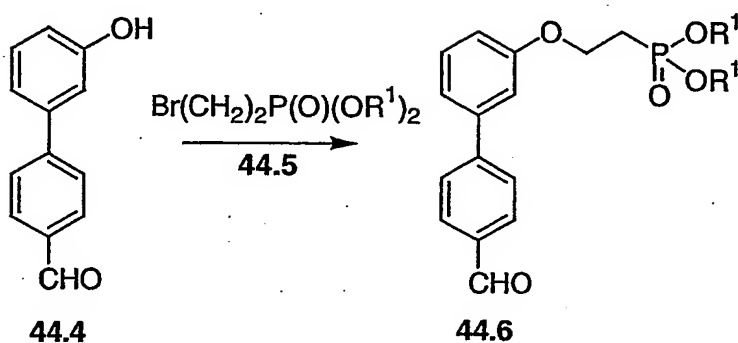
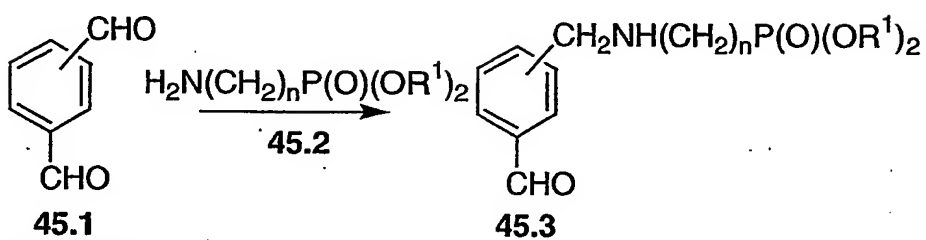
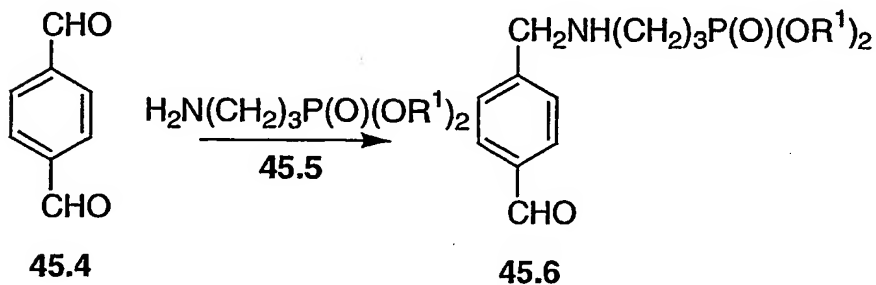
Scheme 43
Method

Example 1



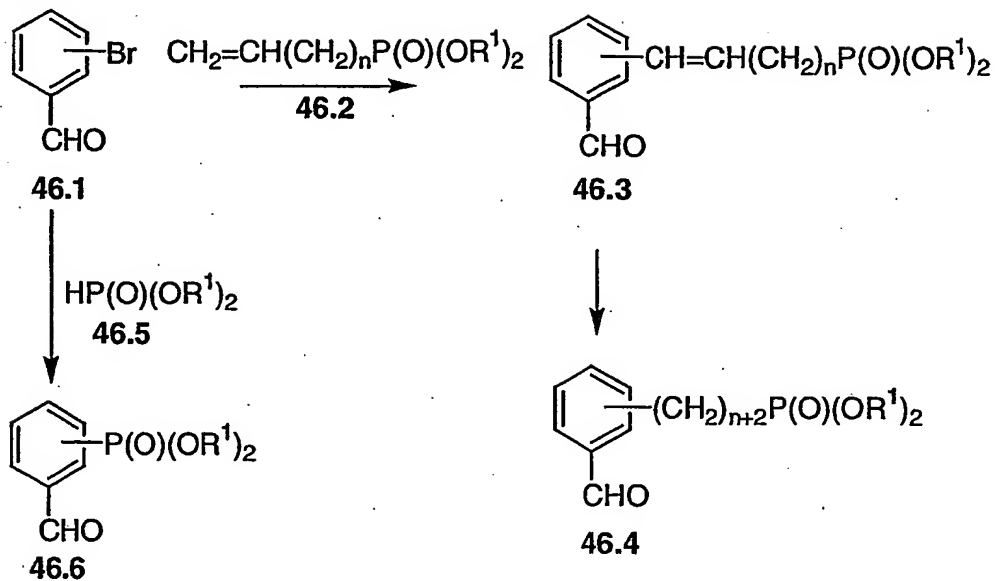
Example 2



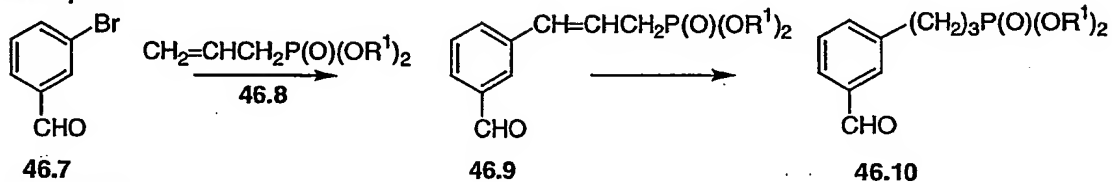
Scheme 44**Method****Example****Scheme 45****Method****Example**

Scheme 46

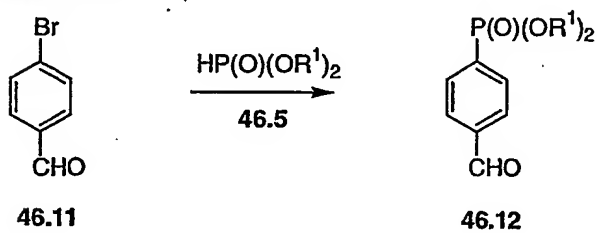
Method



Example 1

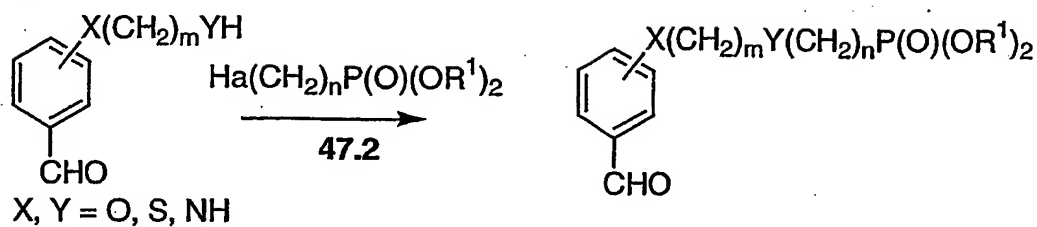


Example 2



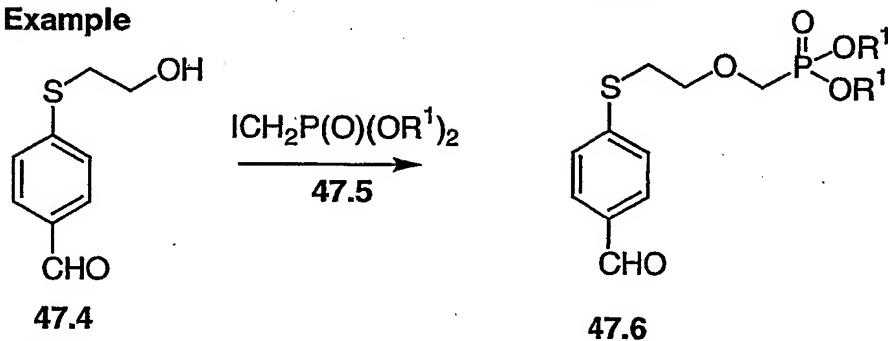
Scheme 47

Method



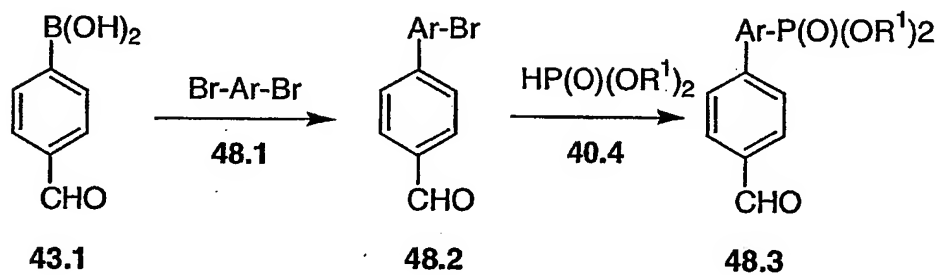
47.1

Example

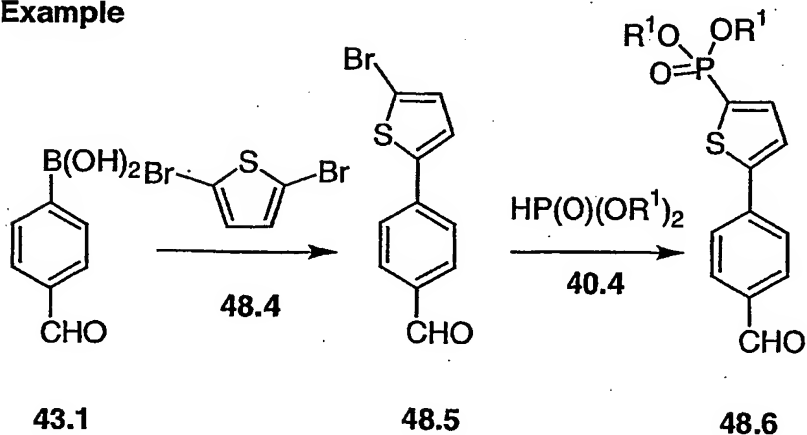


Scheme 48

Method



Example



Preparation of the cyclohexanecarboxaldehyde phosphonates 4.16.

Schemes 49 - 52 illustrate methods for the preparation of the cyclohexanecarboxaldehyde phosphonates 4.16 which are employed in the synthesis of the phosphonate esters 3c.
Scheme 49 depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is attached by means of a nitrogen and an alkylene chain. In this procedure, a cyclohexane dicarboxaldehyde 49.1 is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate 49.2 under reductive amination conditions, as described above, to afford the phosphonate product 49.3.

For example, cyclohexane-1,3-dialdehyde 49.4, the preparation of which is described in J. Macromol. Sci. Chem., 1971, 5, 1873, is reacted with a dialkyl aminopropyl phosphonate 49.5, (Acros) and one molar equivalent of sodium triacetoxyborohydride, to yield the phosphonate product 49.6.
Using the above procedures, but employing, in place of cyclohexane-1,3-dialdehyde 49.4, different cyclohexane dialdehydes 49.1, and /or different aminoalkyl phosphonates 49.2, the corresponding products 49.3 are obtained.

Scheme 50 depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is attached by means of a vinyl or ethylene group and a phenyl ring. In this procedure, a vinyl-substituted cyclohexane carboxaldehyde 50.1 is coupled, in the presence of a palladium catalyst, as described above, (Scheme 36) with a dialkyl bromophenylphosphonate 50.2, to afford the phosphonate product 50.3. Optionally, the product is reduced to afford the ethylene-linked analog 50.4. The reduction reaction is effected catalytically, for example by the use of hydrogen in the presence of a palladium catalyst, or chemically, for example by the use of diimide.

For example, 4-vinylcyclohexanecarboxaldehyde 50.5, the preparation of which is described in WO 9935822, is coupled with a dialkyl 3-bromophenyl phosphonate 50.6, prepared as described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, to give the coupled product 50.7. The product is then reduced with diimide, generated by treatment of disodium azodicarboxylate with acetic acid, as described in J. Am. Chem. Soc., 83, 3725, 1961, to yield the saturated product 50.8.

Using the above procedures, but employing, in place of 4-vinylcyclohexanecarboxaldehyde 50.5, different vinylcyclohexane carboxaldehydes 50.1, and /or different bromophenyl phosphonates 50.2, the corresponding products 50.3 and 50.4 are obtained.

5 Scheme 51 depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is attached by means of an alkylene chain incorporating an oxygen atom. In this procedure, a hydroxymethyl-substituted cyclohexane carboxaldehyde 51.1 is reacted, in the presence of a strong base such as sodium hydride or potassium tert. butoxide, with one molar equivalent of a dialkyl bromoalkyl phosphonate 51.2, to prepare the phosphonate 51.3. The
10 alkylation reaction is conducted in a polar organic solvent such as dimethylformamide, tetrahydrofuran or acetonitrile, at from ambient temperature to about 60°.

For example, 3-(hydroxymethyl)cyclohexanecarboxaldehyde 51.4, prepared as described in WO 0107382, is treated with one molar equivalent of sodium hydride in tetrahydrofuran at 50°, and one molar equivalent of a dialkyl bromoethyl phosphonate 51.5 (Aldrich) to afford
15 the alkylation product 51.6.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)cyclohexanecarboxaldehyde 51.4 different hydroxymethylcyclohexane carboxaldehydes 51.1, and /or different bromoalkyl phosphonates 51.2, the corresponding
20 products 51.3 are obtained.

Scheme 52 depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is directly attached to the cyclohexane ring. In this procedure, a hydroxy-substituted cyclohexanecarboxaldehyde 52.1 is converted into the corresponding bromo derivative 52.2. The conversion of alcohols into the corresponding bromides is described, for example, in
25 Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. The transformation is effected by treatment of the alcohol with hydrobromic acid, or by reaction with hexabromoethane and triphenylphosphine, as described in Synthesis, 139, 1983. The resulting bromo compound 52.2 is then subjected to an Arbuzov reaction, by treatment with a trialkyl phosphite 52.3 at ca 100°. The preparation of phosphonates by mean of the
30 Arbuzov reaction is described in Handb. Organophosphorus Chem., 1992, 115.

For example, 4-hydroxycyclohexanecarboxaldehyde 52.5 is reacted with one molar equivalent of hexabromoethane and triphenyl phosphine in dichloromethane, to yield 4-

bromocyclohexanecarboxaldehyde 52.6. The product is heated at 100° with a trialkyl phosphite 52.3 to afford the cyclohexyl phosphonate 52.7.

Using the above procedures, but employing, in place of 4-

(hydroxymethyl)cyclohexanecarboxaldehyde 52.5, different hydroxy-substituted

5 cyclohexanecarboxaldehydes 52.1, the corresponding products 52.4 are obtained.

Preparation of quinoline 2-carboxylic acids 19a.1 incorporating phosphonate moieties or precursors thereto.

10 The reaction sequence depicted in Schemes 19a - 19d require the use of a quinoline-2-carboxylic acid reactant 19a.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br.

A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino
15 and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het. Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described,
20 for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

25 Scheme 53 illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde 53.1 is reacted with an alkyl pyruvate ester 53.2, in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester 53.3. Hydrolysis of the ester, for example by the use of aqueous base, then
30 afford the corresponding carboxylic acid 53.4. The carboxylic acid product 53.4 in which X is NH₂ can be further transformed into the corresponding compounds 53.6 in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The

conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the

5 diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoroborate, is then heated in aqueous solution, for example as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol 53.6, X = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic

10 Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, 53.6, Y = Br. Alternatively, the diazonium tetrafluoroborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 200, 24, 123, to afford the thiol 53.6, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters 53.3 instead

15 of the carboxylic acids 53.5.

For example, 2,4-diaminobenzaldehyde 53.7 (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate 53.2 in methanol, in the presence of a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate 53.8. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the

20 carboxylic acid 53.9. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoroborate 53.10 by reaction with sodium nitrite and tetrafluoroboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, 53.11, Z = OH. Alternatively, the diazonium tetrafluoroborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-

25 bromoquinoline-2-carboxylic acid 53.11, X = Br. Alternatively, the diazonium tetrafluoroborate 53.10 is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid 53.11, Z = SH.

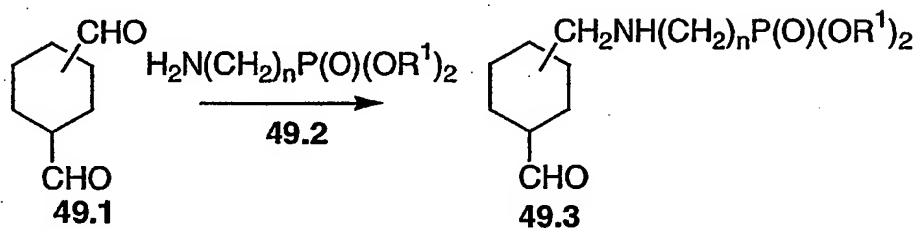
Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde 53.7,

30 different aminobenzaldehydes 53.1, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids 53.6 are obtained. The variously substituted quinoline

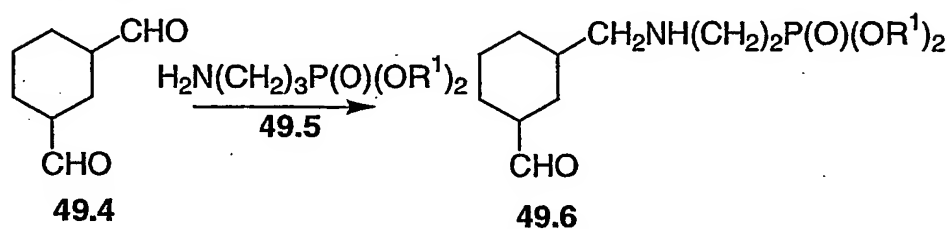
carboxylic acids and esters can then be transformed, as described below, (Schemes 54 – 56) into phosphonate-containing derivatives.

Scheme 49

Method



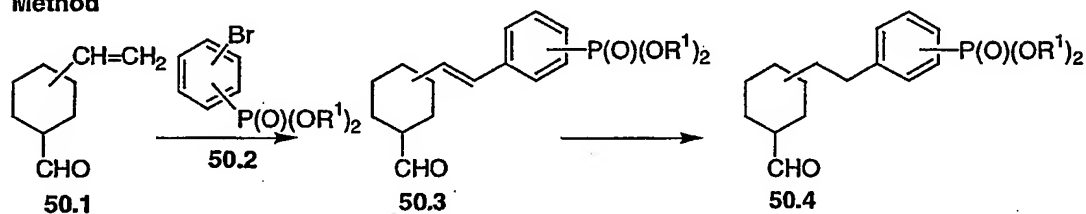
Example



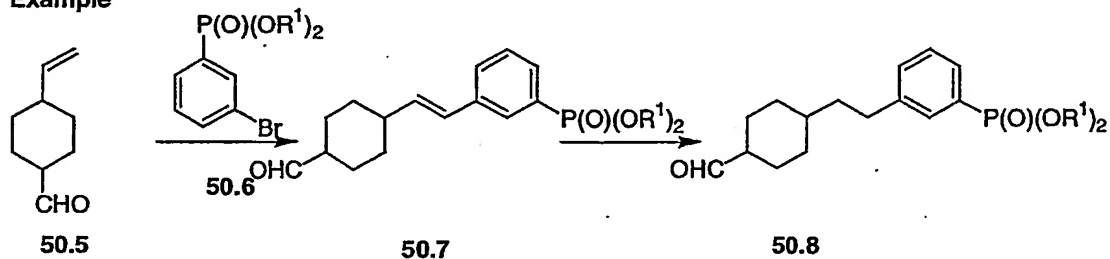
5

Scheme 50

Method

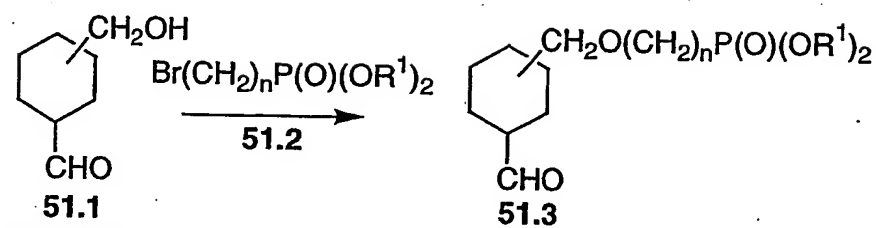


Example

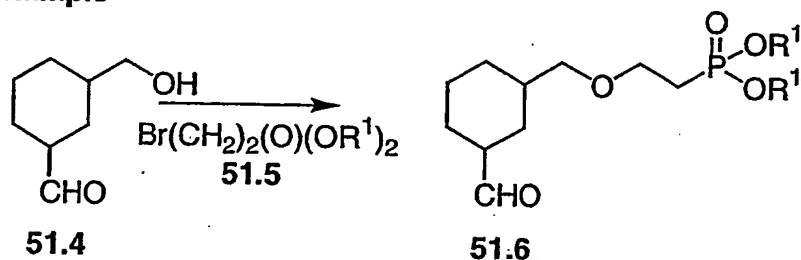


Scheme 51

Method

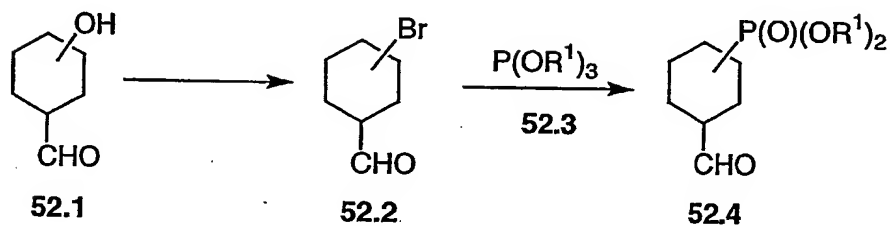


Example

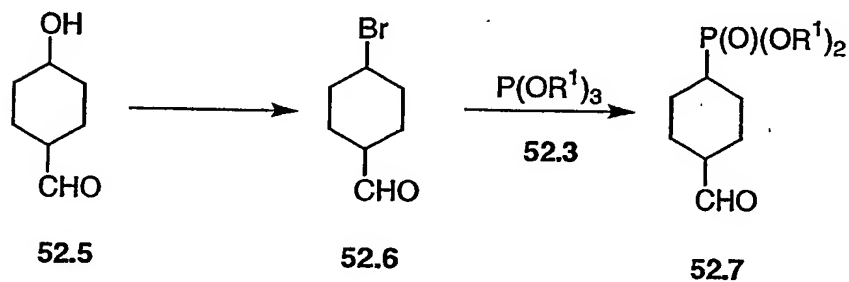


Scheme 52

Method

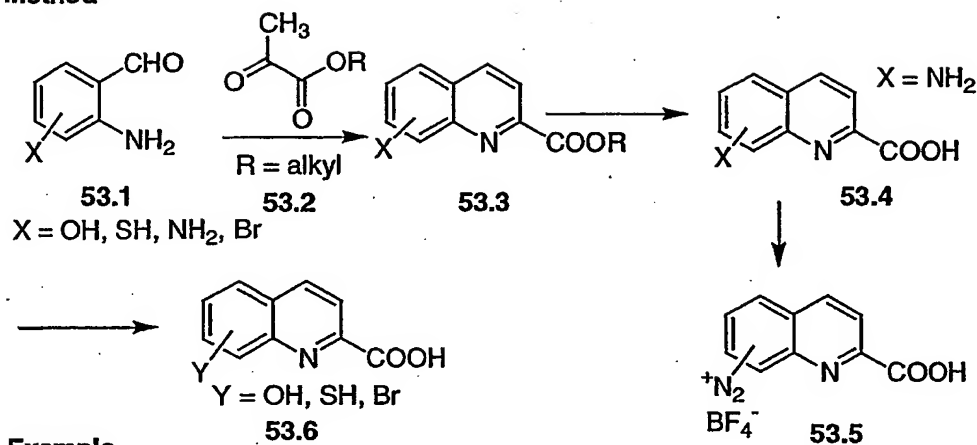


Example

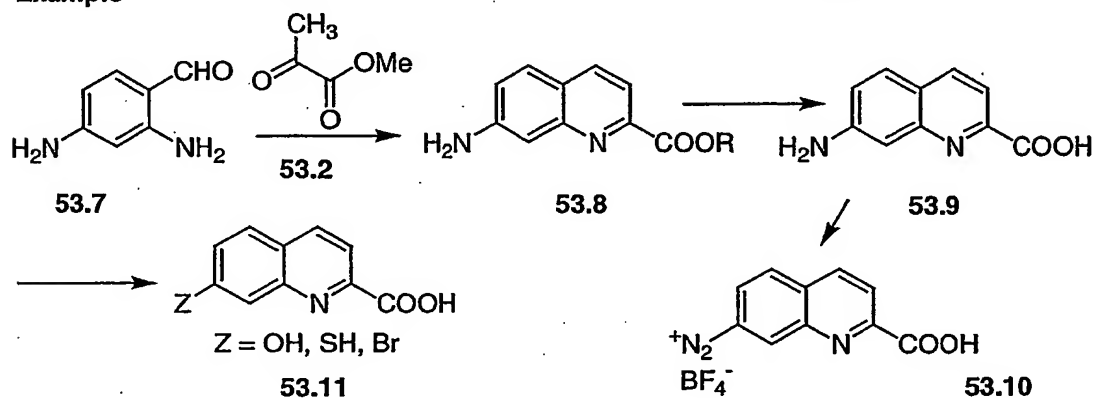


Scheme 53

Method



Example



Scheme 54 depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester 54.1 is transformed, via a diazotization procedure as described above (Scheme 53) into the corresponding phenol or thiol 54.2. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate 54.3, under the conditions of the Mitsunobu reaction, to afford the phosphonate ester 54.4. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the thioether products 54.5. Basic

hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid 54.6.

For example, methyl 6-amino-2-quinoline carboxylate 54.7, prepared as described in J. Het. Chem., 1989, 26, 929, is converted, by means of the diazotization procedure described above,
5 into methyl 6-mercaptoquinoline-2-carboxylate 54.8. This material is reacted with a dialkyl hydroxymethylphosphonate 54.9 (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether 54.10. Basic hydrolysis then afford the carboxylic acid 54.11.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline
10 carboxylate 54.7, different aminoquinoline carboxylic esters 54.1, and/or different dialkyl hydroxymethylphosphonates 54.3 the corresponding phosphonate ester products 54.6 are obtained.

Scheme 55 illustrates the preparation of quinoline-2-carboxylic acids incorporating
15 phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester 55.1 is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate 55.2. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001,
20 p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Thus, Heck coupling of the bromo compound 55.1 and the olefin 55.2 affords the olefinic
25 ester 55.3. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid 55.4. Optionally, the unsaturated carboxylic acid 55.4 can be reduced to afford the saturated analog 55.5. The reduction reaction can be effected chemically, for example by the use of diimide, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5.
30 For example, methyl 7-bromoquinoline-2-carboxylate, 55.6, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60° with a dialkyl vinylphosphonate 55.7 (Aldrich) in the presence of 2 mol% of

tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product 55.8. The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid 55.9. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product 55.10.

Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate 55.6, different bromoquinoline carboxylic esters 55.1, and/or different dialkyl alkenylphosphonates 55.2, the corresponding phosphonate ester products 55.4 and 55.5 are obtained.

Scheme 56 depicts the preparation of quinoline-2-carboxylic acids 56.5 in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate 56.1 is reacted with a phosphonate aldehyde 56.2 under reductive amination conditions, to afford the aminoalkyl product 56.3. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product 56.4 is then hydrolyzed to yield the free carboxylic acid 56.5.

For example, methyl 7-aminoquinoline-2-carboxylate 56.6, prepared as described in J. Amer. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate 56.7 (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product 56.8. The ester is then hydrolyzed, as described above, to yield the carboxylic acid 56.9. Using the above procedures, but employing, in place of the formylmethyl phosphonate 56.2, different formylalkyl phosphonates, and/or different aminoquinolines 56.1, the corresponding products 56.5 are obtained.

Interconversions of the phosphonates R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

Schemes 1 - 56 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may be the same or different. The R¹ groups attached to a phosphonate esters 1-7, or to precursors thereto, may be changed using established chemical transformations. The interconversions
5 reactions of phosphonates are illustrated in Scheme 57. The group R in Scheme 57 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1-7 or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-7. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation
10 and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 57.1 into the corresponding phosphonate monoester 57.2 (Scheme 57, Reaction 1) can be accomplished by a number of methods. For example, the ester 57.1 in which R¹ is an aralkyl group such as benzyl, can be converted into the monoester
15 compound 57.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester 57.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 57.2 can be effected by treatment of the ester 57.1 with a base such as aqueous
20 sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

Phosphonate diesters 57.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 57.2 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, can be converted into the monoester
25 57.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 57.1 or a phosphonate monoester 57.2 into the
30 corresponding phosphonic acid 57.3 (Scheme 57, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc.,

Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 57.2 in which R¹ is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid 57.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester 57.2 in which R¹ is alkenyl such as, for example, allyl, can be converted into the phosphonic acid 57.3 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985.

- 10 Palladium catalyzed hydrogenolysis of phosphonate esters 57.1 in which R¹ is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters 57.1 in which R¹ is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.

- The conversion of a phosphonate monoester 57.2 into a phosphonate diester 57.1 (Scheme 57, Reaction 4) in which the newly introduced R¹ group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate 57.2 is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yl)oxytripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester 57.2 to the diester 57.1 can be effected by the use of the Mitsunobu reaction, as described above (Scheme 54). The substrate is reacted with the hydroxy compound R¹OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester 57.2 can be transformed into the phosphonate diester 57.1, in which the introduced R¹ group is alkenyl or aralkyl, by reaction of the monoester with the halide R¹Br, in which R¹ is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the

phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **57.2** is transformed into the chloro analog $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Macir, eds, Wiley, 1976, p. 17, and the thus-obtained product $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester **57.1**.

A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ can be transformed into a phosphonate monoester $\text{RP}(\text{O})(\text{OR}^1)(\text{OH})$ (Scheme 57, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ **57.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ **57.3** can be transformed into a phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ **57.1** (Scheme 57, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine.

Alternatively, phosphonic acids **57.3** can be transformed into phosphonic esters **57.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70° . Alternatively, phosphonic acids **57.3** can be transformed into phosphonic esters **57.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **57.1**.

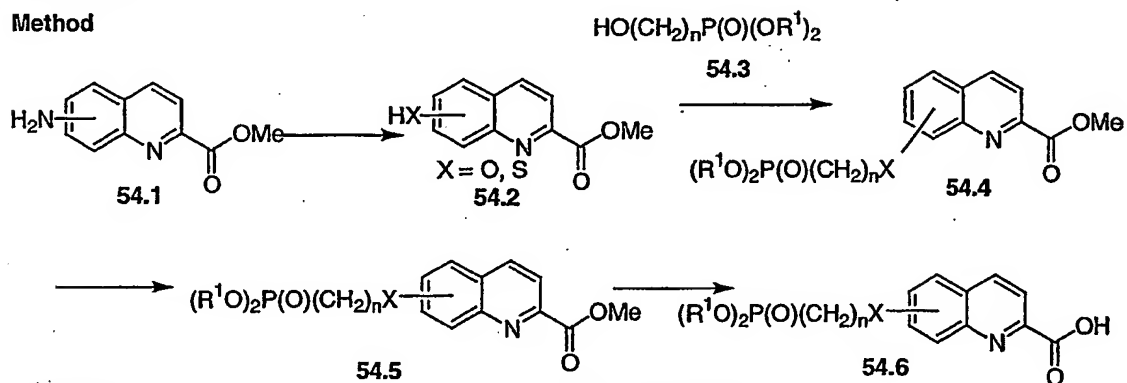
General applicability of methods for introduction of phosphonate substituents.

The procedures described herein for the introduction of phosphonate moieties (Schemes 21 - 56) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into carbinols (Schemes 21 - 26) are applicable to the introduction of phosphonate moieties into the oxirane, thiophenol, aldehyde and quinoline substrates, and the methods described herein for the introduction of phosphonate moieties into the oxirane,

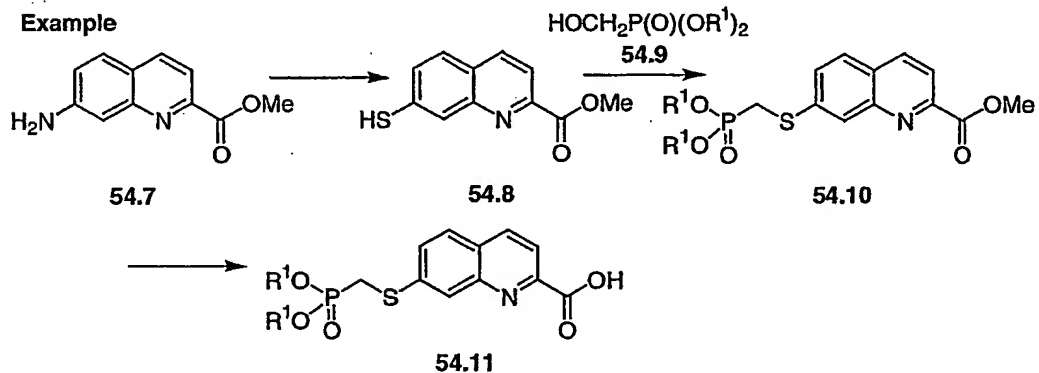
thiophenol, aldehyde and quinoline substrates, (Schemes 27 - 56) are applicable to the introduction of phosphonate moieties into carbinol substrates.

Scheme 54

Method

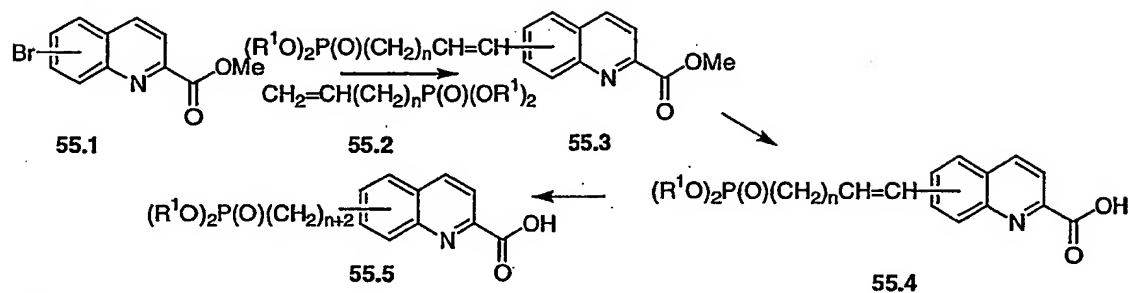


Example

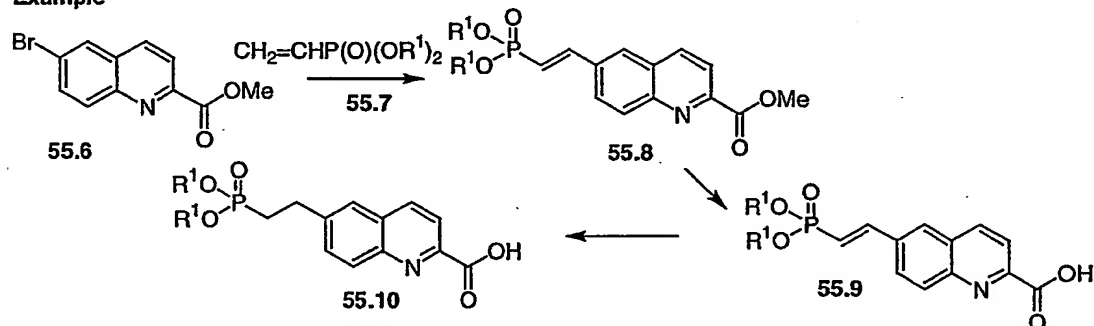


Scheme 55

Method

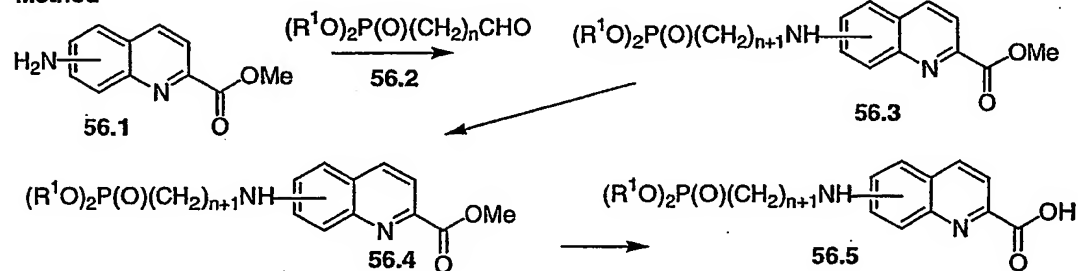


Example

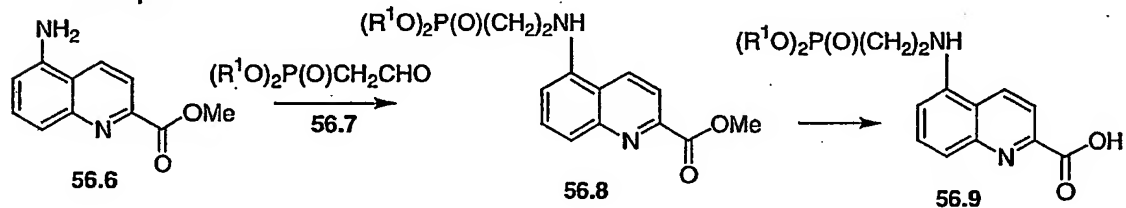


Scheme 56

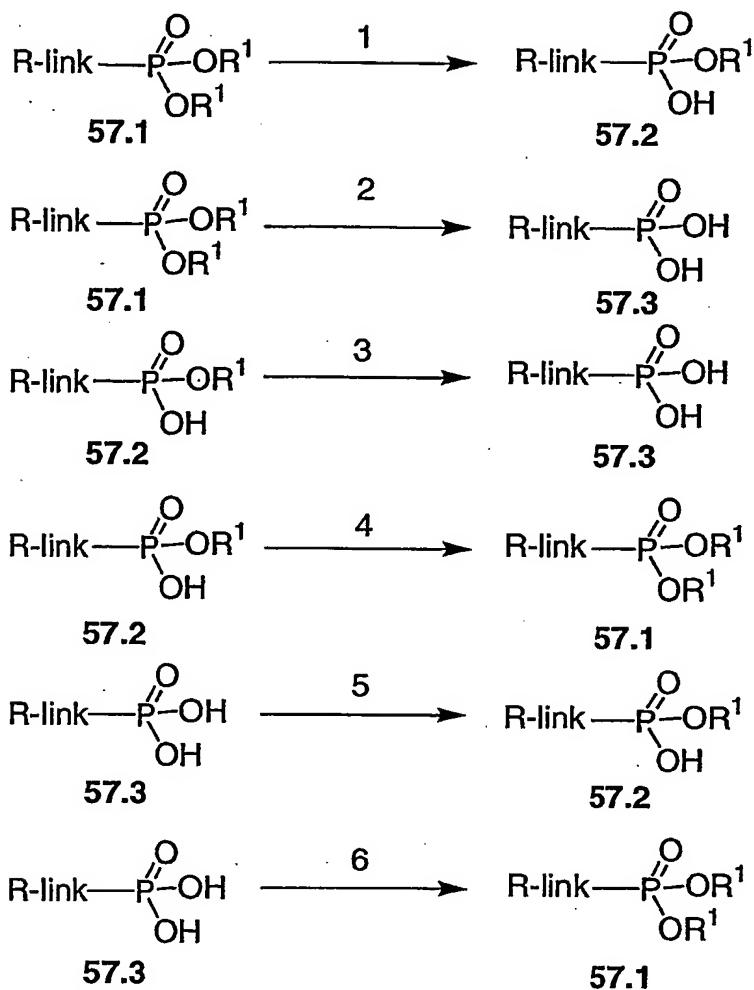
Method



Example



Scheme 57



Preparation of phosphonate intermediates 6 and 7 with phosphonate moieties incorporated into the group R^2COOH and R^5COOH .

5

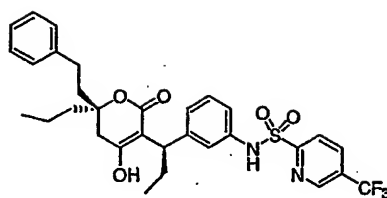
The chemical transformations described in Schemes 1 - 56 illustrate the preparation of compounds 1-5 in which the phosphonate ester moiety is attached to the carbinol moiety, (Schemes 21 - 26), the oxirane moiety (Schemes 27 - 29), the thiophenol moiety (Schemes 30 - 39), the aldehyde moiety (Schemes 40 - 52) or the quinoline moiety (Schemes 53 - 56). The various chemical methods employed for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R^2COOH and R^5COOH , as defined in Charts

10

2a, 2b and 2c. The resultant phosphonate-containing analogs, designated as $R^{2a}COOH$ and $R^{5a}COOH$ can then, using the procedures described above, be employed in the preparation of the compounds 6 and 7. The procedures required for the introduction of the phosphonate-containing analogs $R^{2a}COOH$ and $R^{5a}COOH$ are the same as those described above (Schemes 1, 5, 7 and 10) for the introduction of the R^2CO and R^5CO moieties.

Tipranavir-like phosphonate protease inhibitors (TLPPI)

Chart 1 illustrates the target compounds of the invention. A linkage group (link) is a portion of the structure that links two substructures, one of which is the scaffold having the structures shown above, the other a phosphonate moiety bearing the appropriate R and R^0 groups, as defined below. The link has at least one uninterrupted chain of atoms, other than hydrogen, typically ranging in up to 25 atoms, more preferably less than 10 atoms (hydrogen excluded). The link can be formed using a variety of functional groups such as heteroatom, carbon, alkenyl, aryl etc. Chart 2 illustrates the intermediate phosphonate compounds of this invention that are used in the preparation of the targets, Chart 1. Chart 3 shows some examples illustrated below of linking groups present in the structures in Chart 1 and 2. The R and R^0 groups can be both natural and un-natural amino acid esters linked through the amine nitrogen, or alternatively, one of the groups can be substituted for an oxygen linked aryl, alkyl, aralkyl group etc. Alternatively one of the groups may be an oxygen linked aryl, alkyl, aralkyl group etc and the other a lactate ester.



Tipranavir
US 5852195

Chart 1

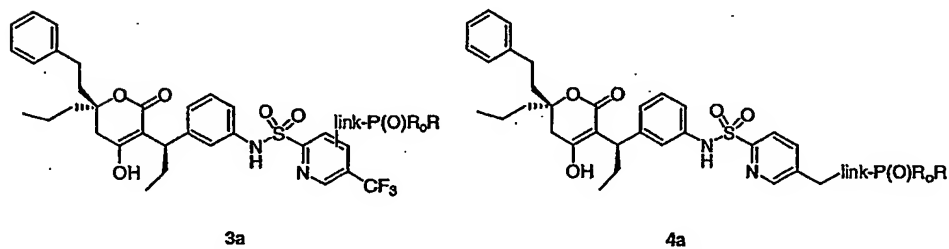
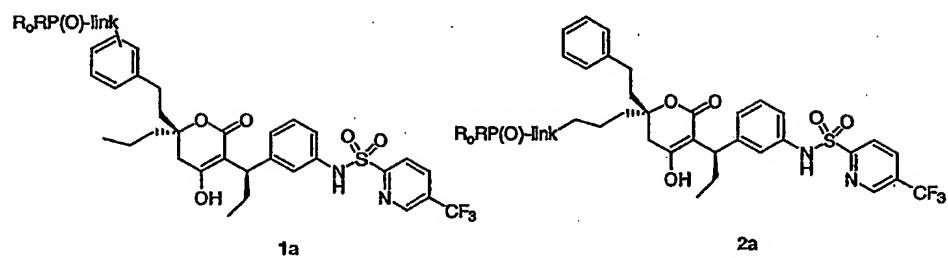
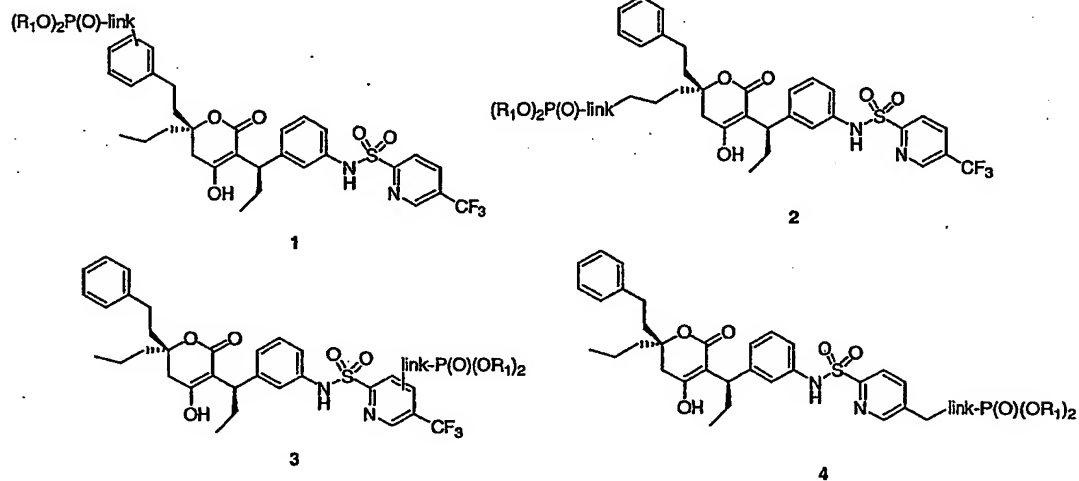
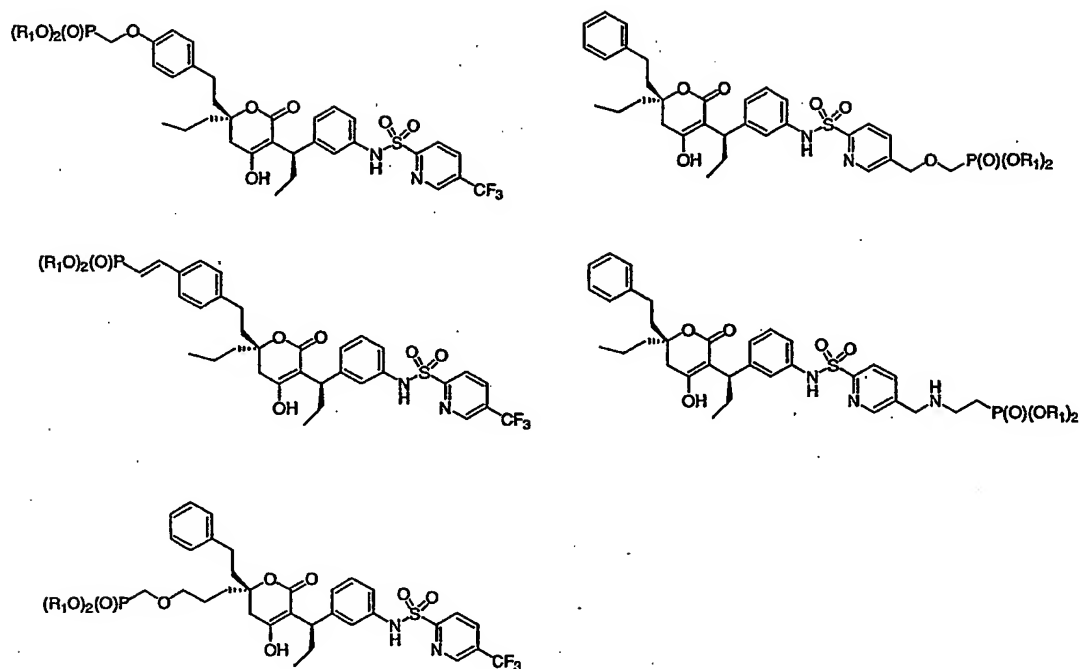


Chart 2



$R_1 = \text{H, alkyl, haloalkyl, alkenyl, aralkyl, aryl}$

Chart 3



Phosphonate Interconversions

The final compounds described above are synthesized according to the methods described in the following Schemes 1-16. The intermediate phosphonate esters are shown in Chart 2 and these compounds can be used to prepare the final compounds illustrated above in Chart 1, by one skilled in the art, using known methods for synthesis of substituted phosphonates. These methods are similar to those described for the synthesis of amides. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274. Further methods are described in Scheme 16 below for the synthesis of the phosphonate diesters and can in some cases be applied to the synthesis of phosphor-amides.

In the following schemes, the conversion of various substituents into the group link- $P(O)(OR^1)_2$, where R^1 is defined in Chart 2, or indeed the final stage of $P(O)RR^0$, as defined above, can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the

substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, amino, during the introduction of the group link-P(O)(OR¹)₂ or P(O)RR^o

In the succeeding examples, the nature of the phosphonate ester group P(O)(OR¹)₂ can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 16). Examples shown in charts 1-3 indicate a specific stereochemistry. However, the methods are applicable to the synthesis all of the possible stereoisomers and the separation of possible isomers can be effected at any stage of the sequence after introduction of the stereocenter. The point in the synthetic sequence would be determined by the resolution that could be achieved in the separation by one skilled in the art.

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], etc.

Preparation of Intermediate Phosphonates shown in Chart 2

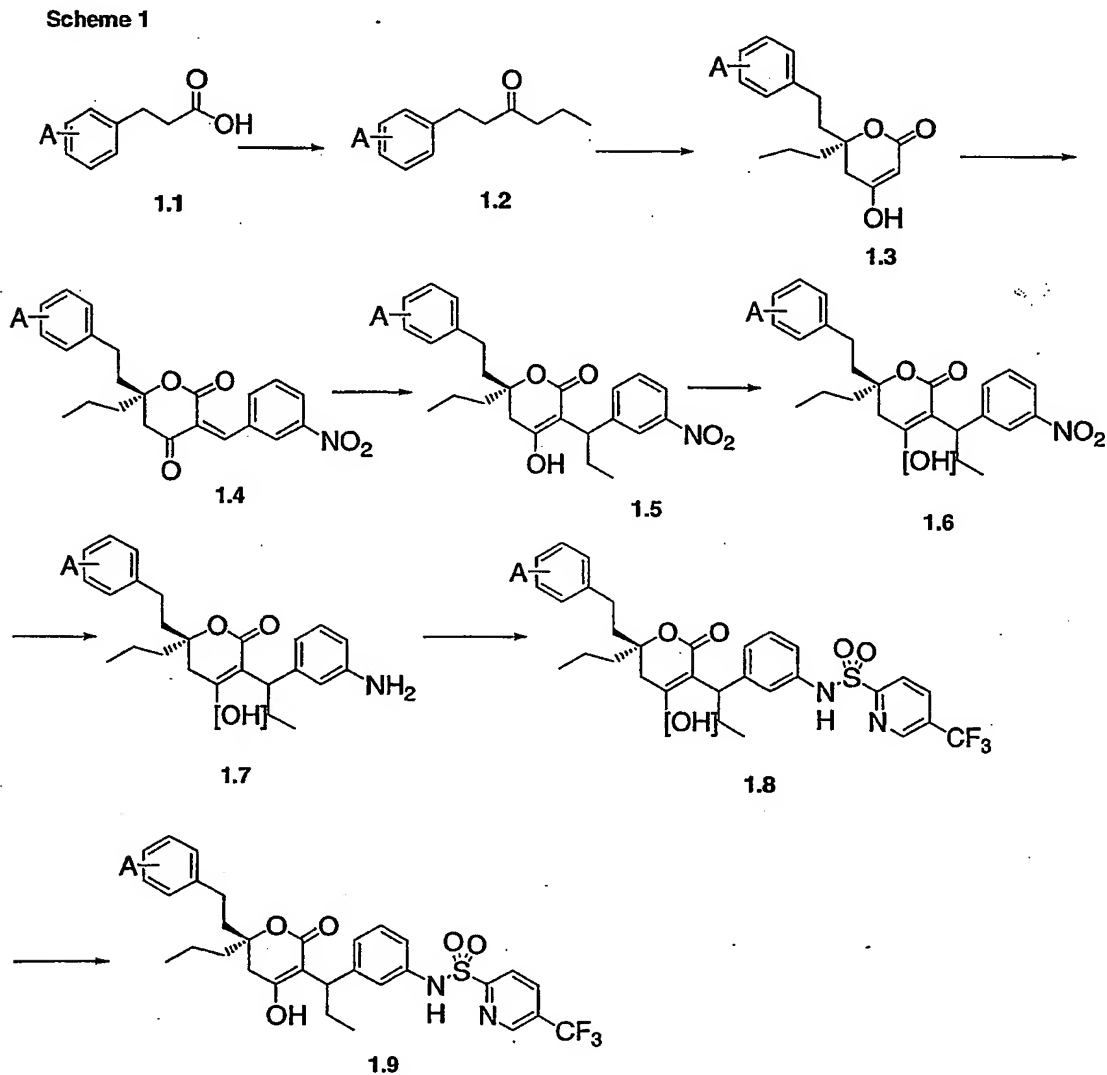
Scheme 1-3 illustrates the synthesis of target molecules of type 1, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂. The procedures described in J. Med. Chem. 1998, 41, p3467 are used to generate compounds of the type 1 from 1.2 in which A is Hydrogen. The conversion of 1.1 into 1.2 follows procedures described in Bioorg Med. Chem 1999, 7, p2775 for the preparation of a similar compound. The preparation of 1.1 is described in Scheme 13-14. For example, acid 1.1 is converted via the Weinreb amide to the ketone 1.2. The ketone 1.2 is then treated with 3-oxo-butyric acid methyl ester, as described in J. Med Chem. 1998, 41, 3467, to give the pyrone 1.3. A mixture of R and S isomers can be carried forward or alternatively separated by chiral chromatography at this stage. Aluminium chloride catalysed condensation of 3-nitrobenzaldehyde onto the pyrone 1.3, as described in J. Med

Chem. 1998, 41, 3467-3476, affords nitro pyrone 1.4. Nitro pyrone 1.4 upon treatment with triethylaluminum in the presence of copper(I) bromide-dimethylsulfide as described in J. Med Chem. 1998, 41, 3467-3476 affords the dihydropyrone 1.5. Protection of the dihydropyran hydroxyl in 1.5 with a suitable protecting group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.249ff gives the hydroxyl protected compound 1.6. For example, treatment with SEMCl in the presence of base e.g. potassium carbonate, generates the SEM ether protected 1.6. Catalytic hydrogenolysis of the nitro group, as described in J. Med Chem. 1998, 41, 3467-3476, affords the aryl amine 1.7 which is then coupled with the 5-trifluoromethyl-pyridine-2-sulfonyl chloride in the presence of pyridine, as described in J. Med Chem. 1998, 41, 3467-3476 to afford the sulfonamide 1.8. Finally, removal of the protecting group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.249ff affords the product 1.9. For example, treatment of the SEM protected product indicated above with TBAF produces the de-silylated (6R, 3R/S) product 1.9. The diastereoisomers are then separated through silica gel chromatography.

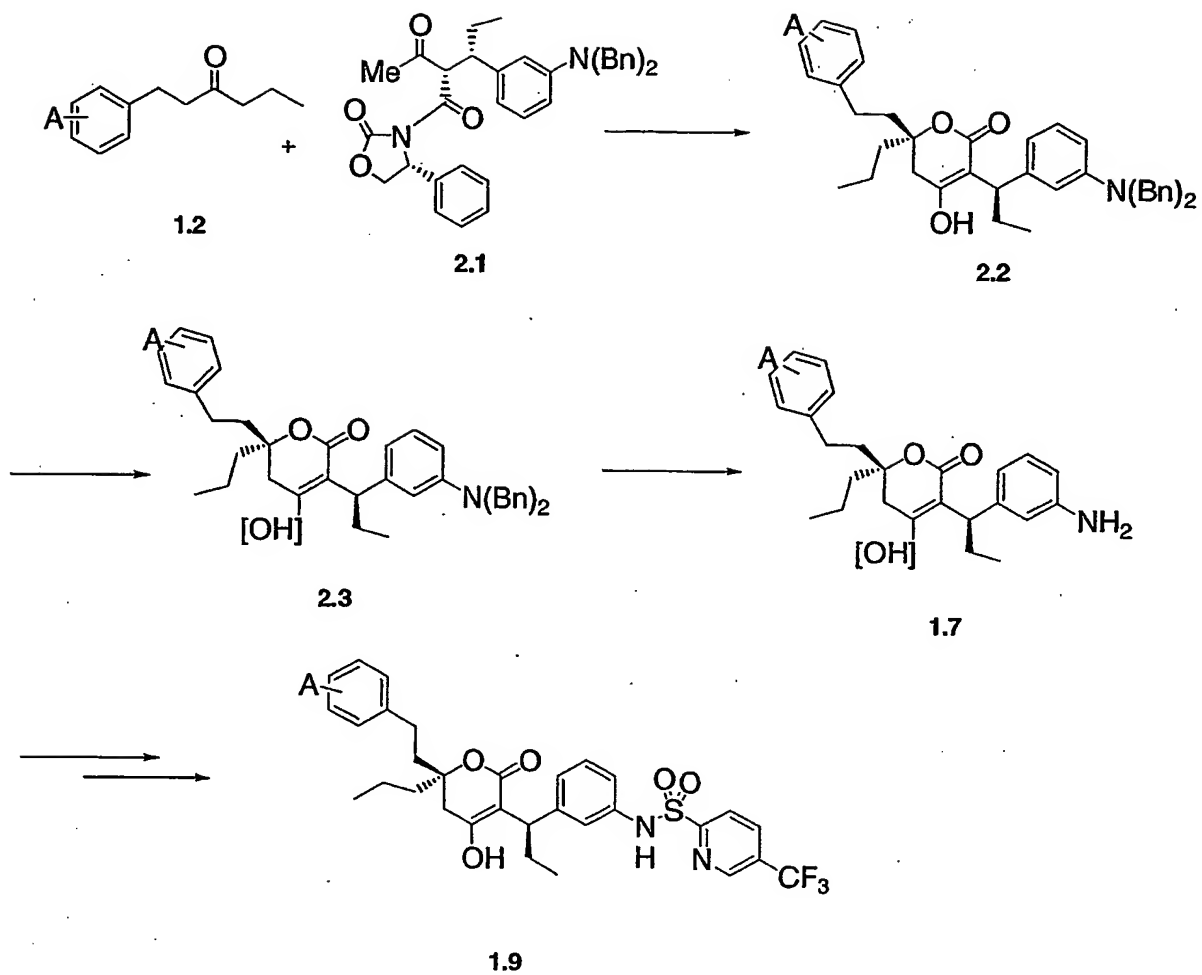
Scheme 2 also illustrates the synthesis of target molecules of type 1, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂ but the products in this example have the absolute stereochemistry (6R, 3R). The ketone 1.2, prepared in Scheme 1, is transformed into the dihydropyrone 2.2 as described in Drugs of the Future, 1998, 23(2), p146. This 2 step reaction involves reaction of the ketone with dioxalone 2.1, prepared as described in Drugs of the Future, 1998, 23(2), p146 in the presence of Ti(OBu)Cl₃, followed by treatment with a base such as potassium tert-butoxide. Treatment of the dihydropyrone 2.2 with the same procedures reported in Scheme 1 for the conversion of 1.5 into 1.9 then affords the final product 1.9 in chiral form (6R, 3R). For example, the pyrone hydroxyl 2.2 is first protected as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.249ff, to afford 2.3 and then the dibenzyl groups are removed from 2.3 by catalytic hydrogenolysis as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.579 to afford the amine product 1.7. Amine 1.7 is then converted into 1.9 as described in Scheme 1.

The reactions shown in Scheme 1-2 illustrate the preparation of the compounds **1.9** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 3 depicts the conversion of the compounds **1.9** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **1**. In this procedure, the compounds **1.9** are

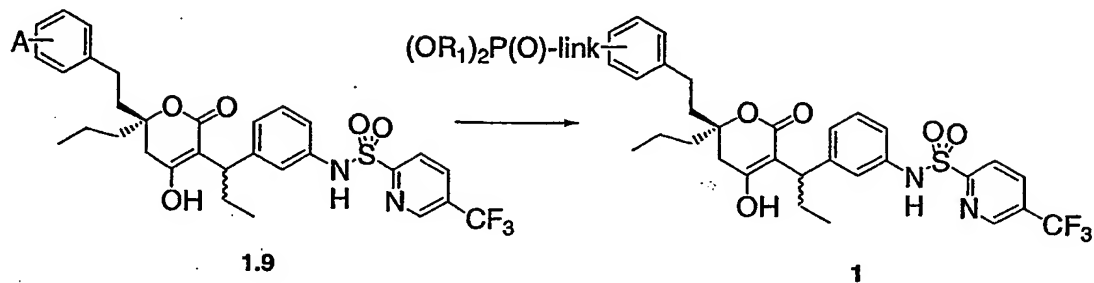
5 converted, using the procedures described below, Schemes 10-15, into the compounds **1**.



Scheme 2



Scheme 3

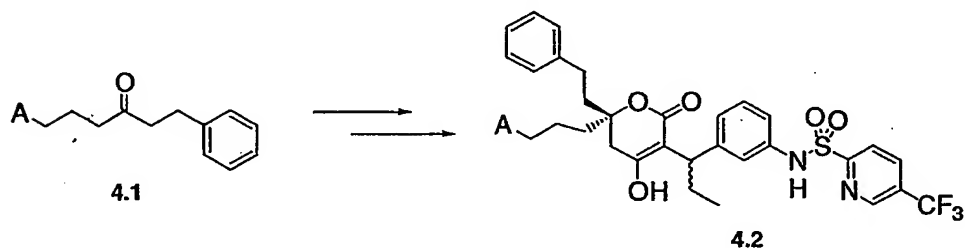


Scheme 4 illustrates the synthesis of target molecules of type 2, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂. The acid 4.1 prepared as described below (Scheme 15), is converted into 4.2 using the procedures described in Scheme 1 or Scheme 2.

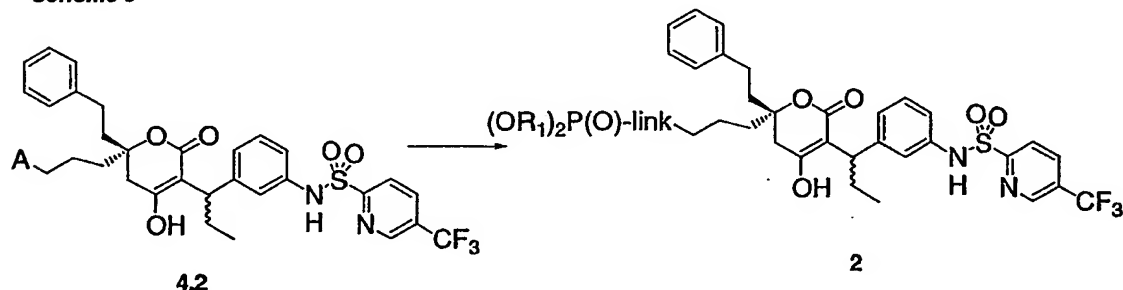
5 The reactions shown in Scheme 4 illustrate the preparation of the compounds 4.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 5 depicts the conversion of the compounds 4.2 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 2. In this procedure, the compounds 4.2 are converted, using the procedures described below, Schemes 10-15, into the compounds 2.

10

Scheme 4



Scheme 5

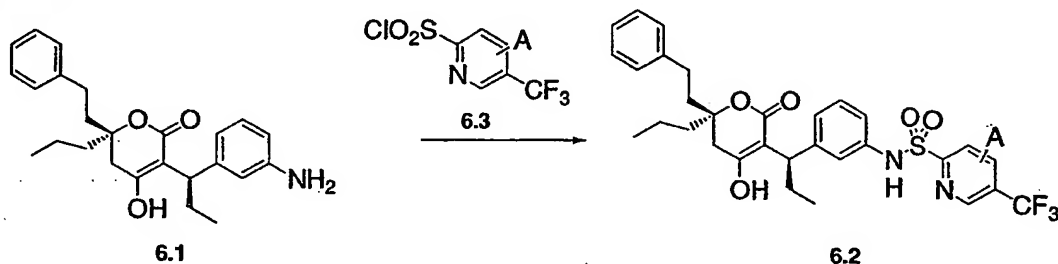


Scheme 6-7 illustrates the synthesis of target molecules of type 3, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂. The amine 6.1 prepared as described in Drugs of the Future, 1998, 23(2), p146 or US 5852195, is converted into the sulfonamide 6.2 using the procedures described in Scheme 1 or Scheme 2 for the preparation of 1.8 from 1.7. The synthesis of the sulfonyl chlorides 6.3 is shown below in Schemes 11-12.

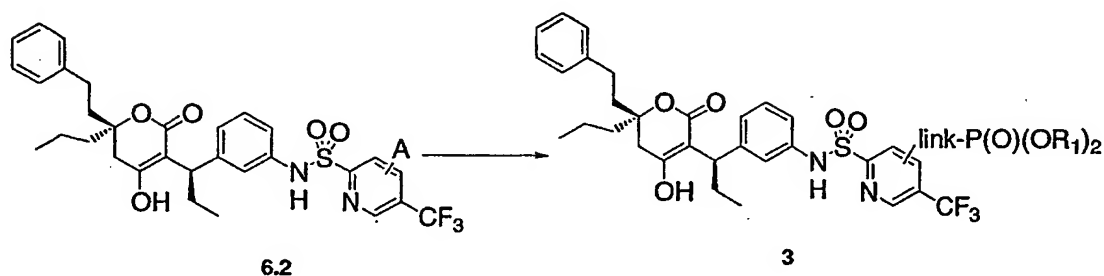
20 The reactions shown in Scheme 6 illustrate the preparation of the compounds 6.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 7 depicts the conversion of the compounds 6.2 in which A is [OH], [SH], [NH],

Br etc, into the phosphonate esters 3. In this procedure, the compounds 6.2 are converted, using the procedures described below, Schemes 10-15, into the compounds 3.

Scheme 6



Scheme 7



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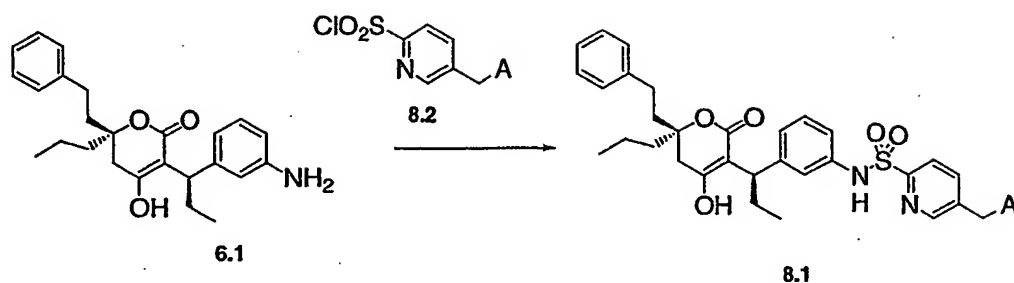
Scheme 8 illustrates the synthesis of target molecules of type 4, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂. The amine 6.1 prepared as described in Drugs of the Future, 1998, 23(2), p146 or US 5852195, is converted into the sulfonamide 8.1 by treatment with 8.2 using the procedures described in Scheme 1 or Scheme 2. The synthesis of the sulfonyl chlorides 8.2 is shown below in Scheme 10.

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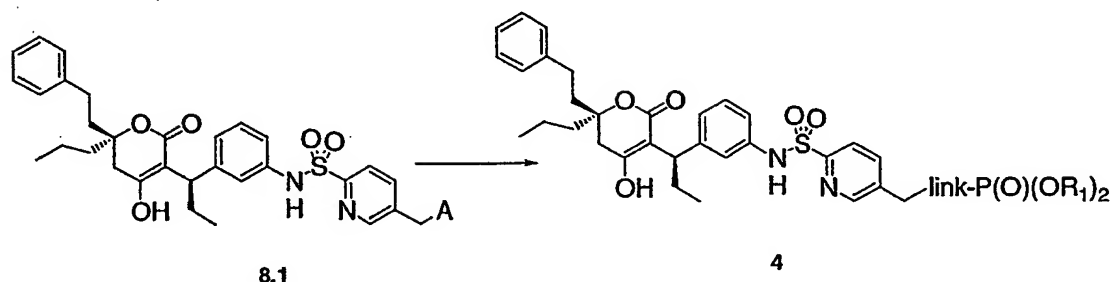
The reactions shown in Scheme 8 illustrate the preparation of the compounds 8.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 9 depicts the conversion of the compounds 8.1 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 4. In this procedure, the compounds 8.1 are converted, using the procedures described below, Schemes 10-15, into the compounds 4.

15

Scheme 8



Scheme 9



Preparation of phosphonate reagents used in the synthesis of compounds 1-4

- 5 Schemes 10 describes the preparation of phosphonate-containing derivatives 8.2, in which the phosphonate is linked through a heteroatom, which are employed in the preparation of the phosphonate ester intermediates 4. The pyridyl ester 10.1 (Acros) is first reduced to the alcohol 10.2. This transformation involves reducing the ester with lithium aluminium hydride, or other reducing agent, in an inert solvent such as THF or dioxane. Alcohol 10.2 is then
- 10 converted to the bromide 10.3 through typical hydroxyl to bromide conversion conditions described in Comprehensive Organic Transformations, R.C. Larock, 2nd edition, p693-697. For instance, treatment of 10.2 with carbon tetrabromide and triphenylphosphine in THF or dioxane affords the bromide 10.3. Treatment of the bromide 10.3 with a thiol, amino, or hydroxyl alkyl phosphonate 10.6 then affords the phosphonate product 10.4. The reaction is
- 15 performed in the presence of a base, in a polar aprotic solvent such as dioxane or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant 10.6. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. The chloride 10.4 is then treated KHS in
- 20 methanol, as described in Justus Liebigs Annalen Chemie, 1931, p105 or thiourea followed by

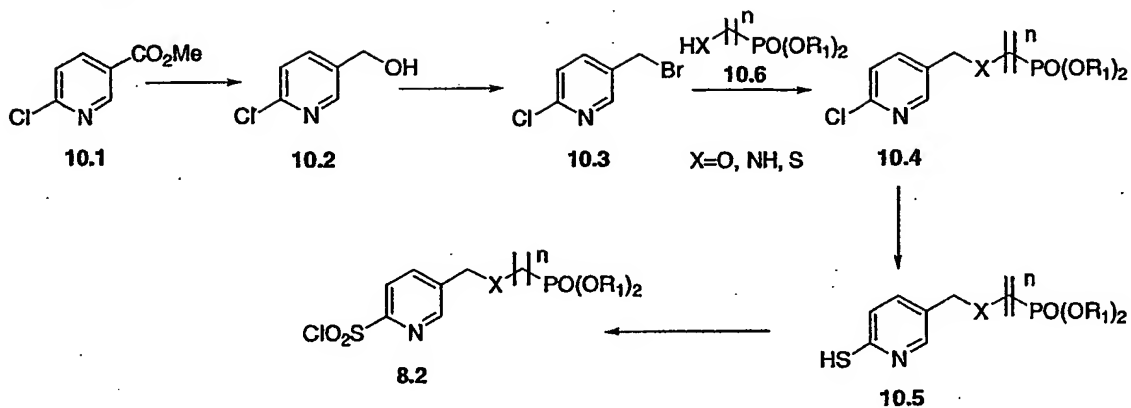
potassium hydroxide treatment, as described in Heterocycles 1984, p117, to give the α -sulfide 10.5. If appropriate, reactive groups e.g. amines in the phosphonate chain, are protected using methods known to one skilled in the art. The α -sulfide 10.5 is then converted to the sulfonyl chloride 8.2 by treatment with chlorine in HCl, as described in Synthesis 1987, 4, p409, or J. Med. Chem 1980,12, p1376.

For example, the pyridyl bromide 10.3, described above, is treated with amino phosphonate 10.7, prepared as described in J. Org. Chem. 2000, 65, p676, in the presence of potassium carbonate and DMF to afford the phosphonate product 10.8. Protection of the amine by conversion to the CBZ carbamate 10.9 is performed by treatment of 10.8 with benzyl chloroformate in the presence of triethylamine. Further treatment of 10.9 with thiourea in ethanol at reflux followed by treatment with potassium hydroxide in water then affords the thiol 10.10. Thiol 10.10 is then treated with chlorine in HCl (aqueous) to afford the sulfonyl chloride 10.11. Using the above procedures, but employing, in place of the amino alkyl phosphonate 10.7, different alkyl phosphonates 10.6, the corresponding products 8.2 are obtained.

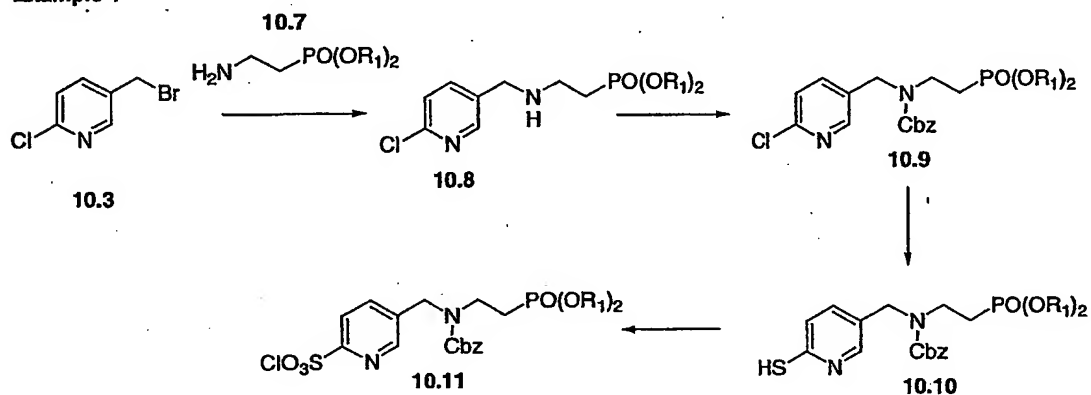
Alternatively (Example 2), illustrates the preparation of phosphonates in which the link is through an oxygen atom. The pyridyl bromide 10.3 described above, is treated with hydroxyl phosphonate 10.12, prepared as described in Synthesis 1998, 4, p327, in the presence of potassium carbonate and DMF to afford the phosphonate product 10.13. Further treatment of 10.13, as described above, for the conversion of 10.8 into 10.11 affords the sulfonyl chloride 10.16. Using the above procedures, but employing, in place of the hydroxy alkyl phosphonate 10.12, different alkyl phosphonates 10.6 the corresponding products 8.2 are obtained.

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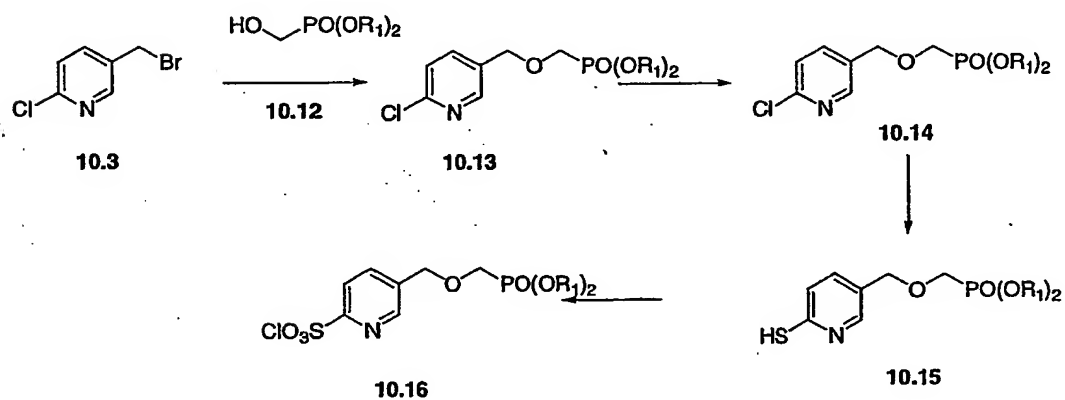
Scheme 10



Example 1



Example 2



- 5 Schemes 11-12 describe the preparation of phosphonate-containing derivatives 6.3, which are employed in the preparation of the phosphonate ester intermediates 3. Scheme 11 illustrates compounds of type 6.3 in which the link is through a oxygen, sulfur or nitrogen heteroatom.

Pyridyl halide 11.1 is treated with the dialkyl hydroxy, thio or amino-substituted alkylphosphonate 10.6 to give the product 11.3. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant 10.6. For example, if X is O, a strong
5 base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. Upon formation of 11.3 the pyridine is converted to the α -chloro pyridine 11.4 by treatment with chlorine at high temperature in a sealed vessel as described in Recl. Trav. Chim
10 Pays-Bas 1939, 58, p709 or, preferably, the α -chloro compound is generated by treatment of 11.3 with butyl lithium in hexane and $\text{Me}_2\text{N}(\text{CH}_2)_2\text{OLi}$ followed by addition of a chloride source such as hexachloroethane, as described in Chem Commun. 2000, 11, p951. Chloride 11.4 is then converted to the thiol 11.4 as described above (Scheme 10). Thiol 11.5 is then converted to the sulfonyl chloride 6.3 as described in Scheme 10.

15 For example, bromo pyridine (Apollo) 11.6 is treated with amine 10.7 in the presence of cesium carbonate in THF or alternative solvent at reflux to give the amine 11.7. The amine is then converted to the sulfonyl chloride 11.9 through the intermediate chloride 11.8 as described in Scheme 10. Using the above procedures, but employing, in place of the amino alkyl phosphonate 10.7, different alkyl phosphonates 10.6, and in place of the pyridine 11.6
20 different halo pyridines 11.1, the corresponding products 6.3 are obtained.

Alternatively the bromo pyridine 11.6 (Apollo) is treated with thiol 11.10, prepared as described in Zh. Obschei. Khim 1973, 43. p2364, in the presence of cesium carbonate in THF or alternative solvent at reflux to give the thiol 11.11. The thiol is then converted to the
25 sulfonyl chloride 11.12 as described above for the conversion of 11.7 into 11.9. Using the above procedures, but employing, in place of the thiol alkyl phosphonate 11.10, different alkyl phosphonates 10.6, and in place of the pyridine 11.6 different halo pyridines 11.1, the corresponding products 6.3 are obtained.

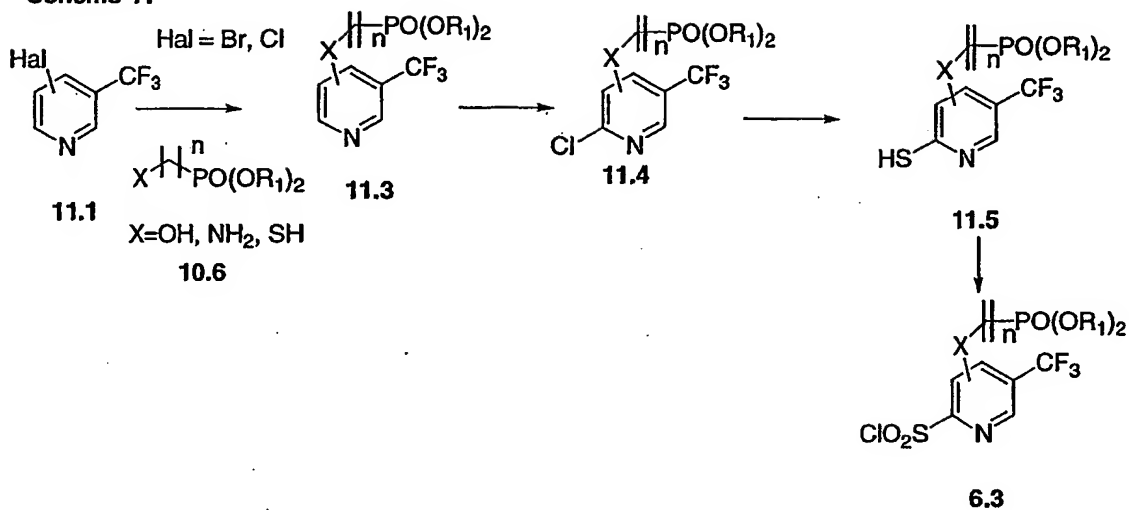
30 Scheme 12 illustrates compounds of type 6.3 in which the phosphonate is attached through an unsaturated or saturated carbon linker. In this procedure, pyridyl bromo compound 11.1 is treated under a palladium catalyzed Heck coupling conditions with the alkene 12.1 to give the

coupled alkene 12.2. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxane, in the presence of
5 a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product 12.2. Optionally, the product 12.2 can be reduced to afford the saturated phosphonate 12.4. Methods for the reduction of carbon-carbon double bonds are described, for example, in *Comprehensive*
10 *Organic Transformations*, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, and chemical reduction, the latter for example employing diborane or diimide. Following the Heck reaction or reduction the pyridyl compounds 12.2 and 12.4 are converted to the sulfonyl chlorides 12.3 and 12.5 respectively, using the same procedures described in Scheme 11 for the conversion of 11.3 into 6.3

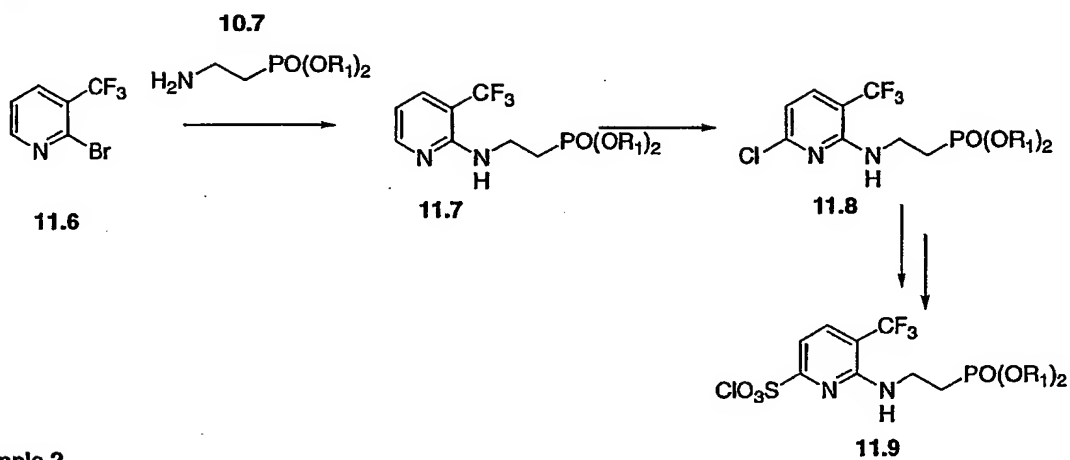
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For example, pyridine 11.6 (Aldrich) is reacted with a dialkyl propenyl phosphonate 12.6, the preparation of which is described in *J. Med. Chem.*, 1996, 39, 949, in the presence of bis(triphenylphosphine) palladium(II) chloride, as described in *J. Med. Chem.*, 1992, 35, 1371, to afford the coupled product 12.7. The product 12.7 is then reduced, for example by
20 reaction with diimide, as described in *J. Org. Chem.*, 30, 3965, 1965, to afford the saturated product 12.9. Conversion of the products 12.7 and 12.9 into the sulfonyl chlorides 12.8 and 12.10 respectively follows the same procedures described above for the conversion of pyridine 11.7 into 11.9. Using the above procedures, but employing, in place of the halo pyridine compound 11.6, different pyridines 11.1, and/or different phosphonates 12.1 in place of 12.6,
25 the corresponding products 12.3 and 12.5 are obtained.

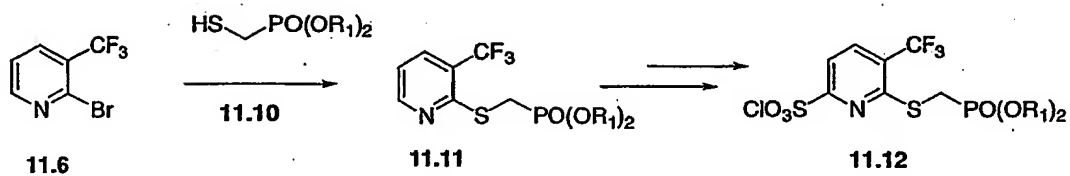
Scheme 11



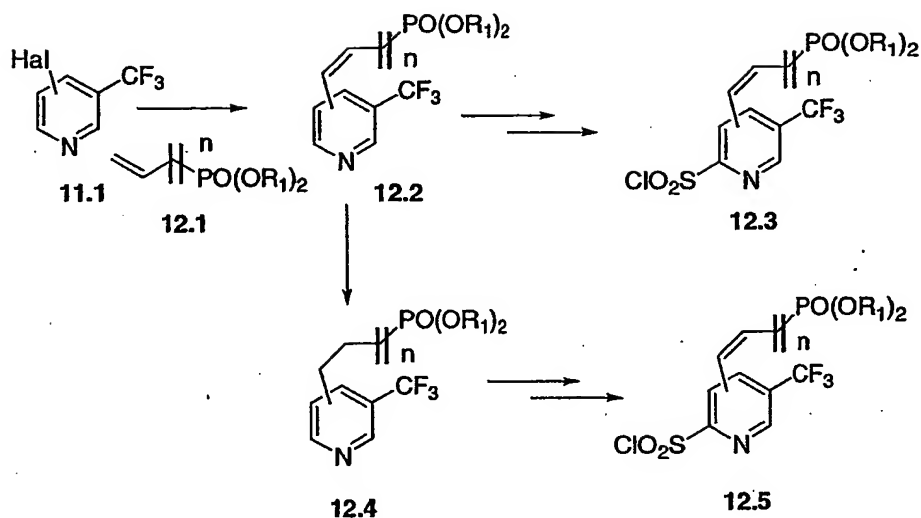
Example 1



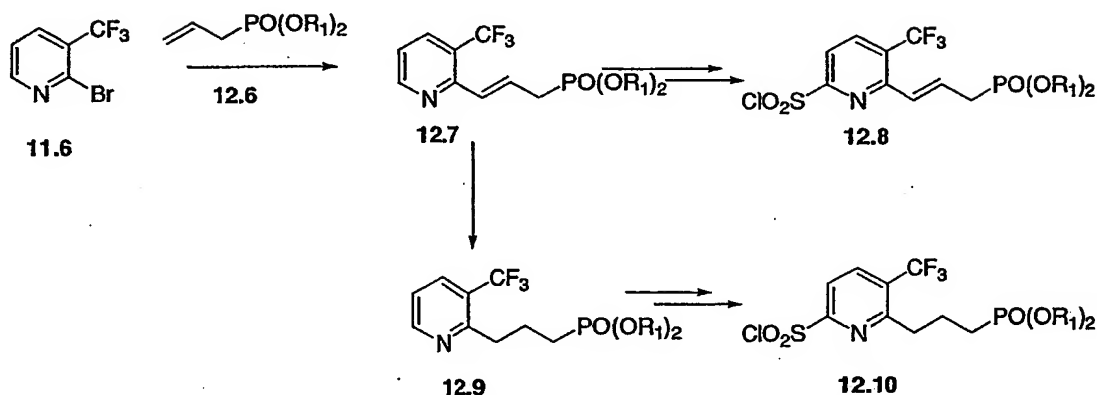
Example 2



Scheme 12



Example 1



- 5 Schemes 13-14 illustrate the preparation of phosphonate containing compounds 1.1 that are used in the preparation of the compounds of type 1, chart 2. Scheme 13 illustrates the preparation of phosphonates 1.1 in which the phosphonate is attached through a heteroatom such as S, O or N. The aryl halide 13.1 bearing a hydroxyl, amino or thiol group, is treated with one equivalent of the phosphonate alkylating agent 13.2, in which Lv is a group such as mesyl, trifluoromethanesulfonyl, Br, I, Cl, tosyl etc, in the presence of base e.g. potassium or cesium carbonate in DMF, to give the compound 13.3. The product 13.3 is then converted to the alkene 13.4 using a palladium mediated Heck coupling with Methyl acrylate as described
- 10

above, Scheme 12. The acrylate is reduced as described in Scheme 12 and then the ester is hydrolyzed by treatment with base such as lithium or sodium hydroxide to afford the acid 1.1.

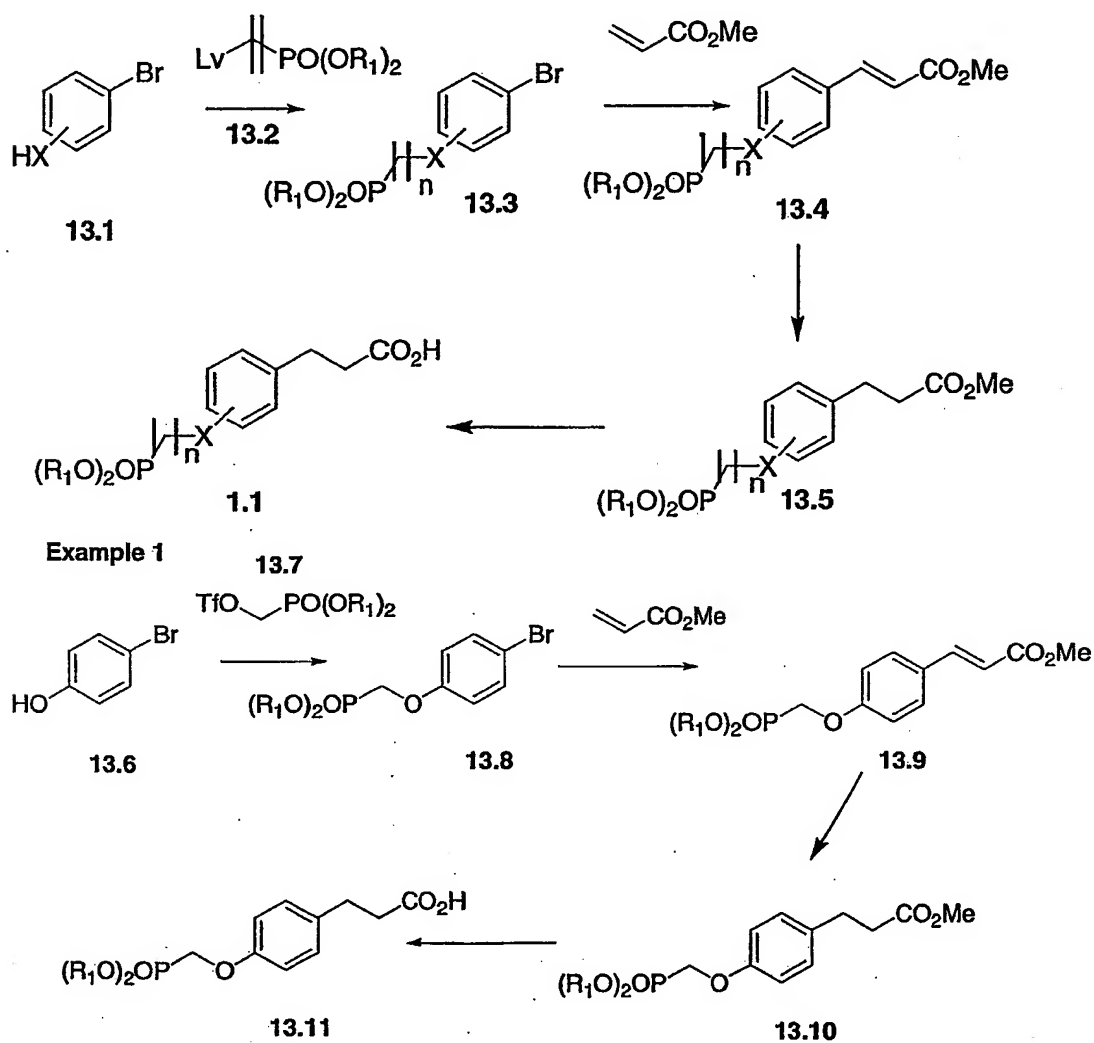
For example, the halide 13.6 (Aldrich) is treated with triflate phosphonate 13.7, prepared as described in Tet. Lett. 1986, 27, p1497, and potassium carbonate in DMF, to give the ether 13.8. The ether is then treated with methyl acrylate under Heck coupling conditions as described in J. Med. Chem. 1992, 35, p1371, to give the alkene 13.9. 13.9 is reduced by treatment with diimide, as described analogously in Bioorg Med. Chem. 1999, 7, p2775 to give the saturated aryl ester 13.10. Treatment of 13.10 with lithium hydroxide in THF and water then affords the acid 13.11. Using the above procedures, but employing, in place of the aryl halide 13.6, different aryl halides 13.1, and/or different phosphonates 13.2 in place of 13.7, the corresponding products 1.1 are obtained.

Scheme 14 illustrates the preparation of phosphonates 1.1 in which the link is through a carbon bond and a nitrogen heteroatom. The aryl halide bearing an carbonyl group is treated with one equivalent of the amino alkyl phosphonate 14.2 under reductive amination conditions to give the amine 14.3. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, 2nd edition, p. 835. In this procedure, the amine component and the aldehyde component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product 14.3. The amine product 14.3 is then converted to the alkene 14.4 using a palladium mediated Heck coupling with Methyl acrylate as described above, Scheme 13. The acrylate is then reduced as described in Scheme 13 to give 14.5, and then the ester is hydrolyzed by treatment with base such as lithium or sodium hydroxide to afford the acid 1.1.

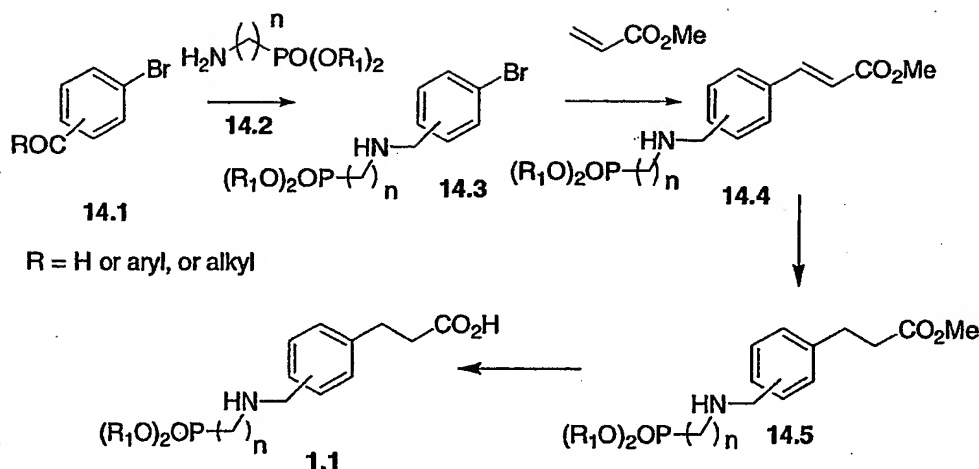
For example, the halide 14.6 (Aldrich) is treated with amino phosphonate 10.7, prepared as described above, in methanol for 30 min. After 30 min sodium borohydride is added to give the amine 14.7. The amine 14.7 is then treated with methyl acrylate under Heck coupling conditions as described above, to give the alkene 14.8. Alkene 14.8 is reduced as described in Scheme 13 to give the saturated ester 14.9. Treatment of 14.9 with lithium hydroxide in THF and water then affords the acid 14.10. Using the above procedures, but employing, in place of

the aryl halide **14.6**, different aryl halides **14.1**, and/or different amino phosphonates **14.2** in place of **10.7**, the corresponding products **1.1** are obtained.

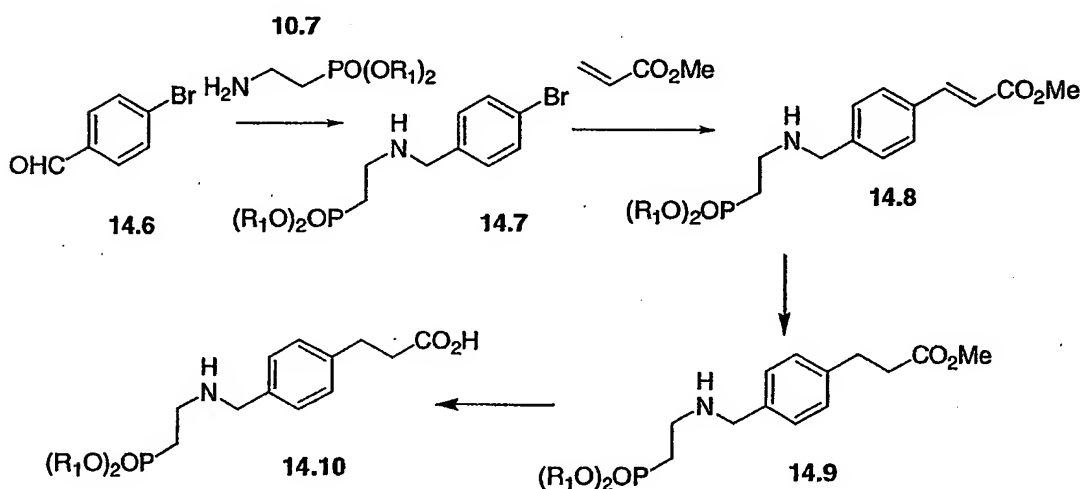
Scheme 13



Scheme 14



Example 1



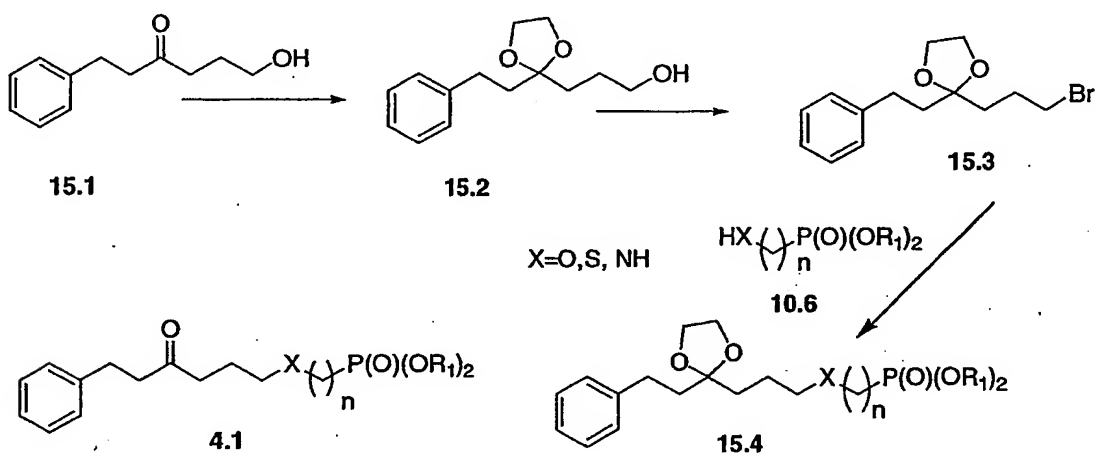
5 Scheme 15 describes the preparation of phosphonate-containing derivatives 4.1 which are employed in the preparation of the phosphonate ester intermediates 2, chart 2. The alcohol 15.1 prepared as described in J. Org Chem. 1994, 59, p3445, is treated with ethylene glycol and a catalytic amount of tosic acid in benzene at reflux to give the 1,3-dioxalane 15.2. The dioxalane is then treated with carbon tetrabromide and triphenyl phosphine in acetonitrile, or

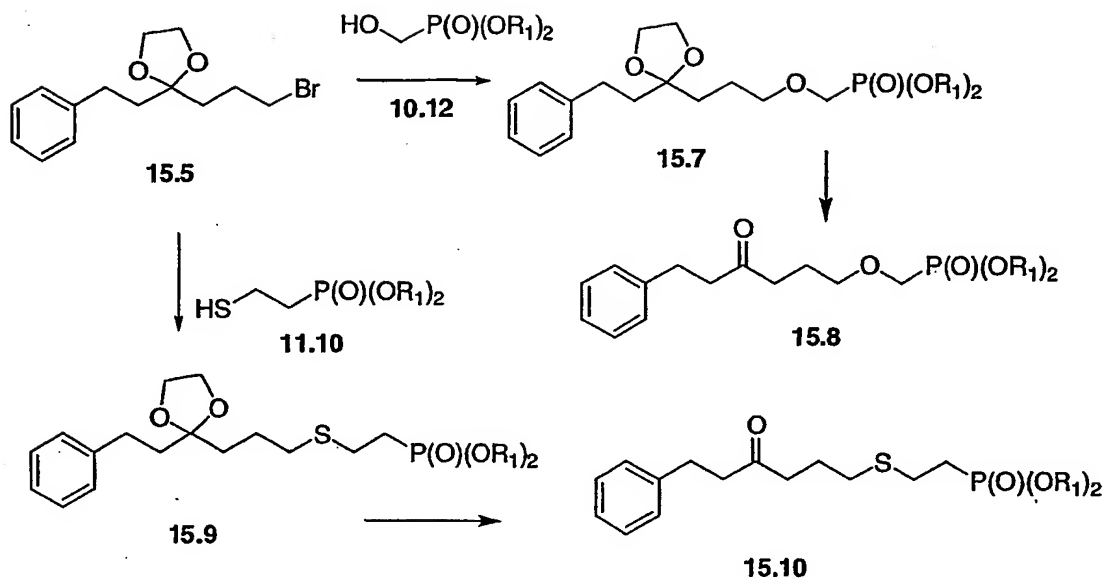
10 alternate conditions as described in Comprehensive Organic Transformations, R.C. Larock, 2nd editions, p693-697, to generate the bromide 15.3. Bromide 15.3 is then treated with the dialkyl hydroxy, thio or amino-substituted alkylphosphonate 10.6 to give the product 15.4. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan

or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant **10.6**. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. Following preparation of **15.4** the dioxalone is removed as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.317.

For example, **15.5** described above, is treated with alcohol **10.12**, prepared as described in Scheme 10, in DMF and potassium carbonate at ca 80 °C to give the phosphonate **15.7**. Alternatively bromide **15.5** is then heated at reflux with an equimolar amount of a dialkyl 2-mercaptoethylphosphonate **11.10**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, in the presence of sodium carbonate, to afford the thioether product **15.9**. Treatment of **15.7** and **15.9** with aqueous HCl in THF then affords the ketones **15.8** and **15.10** respectively. Using the above procedures, but employing, in place of **10.12** and **11.10**, different alkyl phosphonates **10.6** the corresponding products, **4.1** are obtained.

Scheme 15



Example 1**General applicability of methods for introduction of phosphonate substituents.**

The procedures described for the introduction of phosphonate moieties (Schemes 10-15) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, for example, the methods described above for the introduction of phosphonate groups onto the pyridyl ring of **11.1**, are also applicable to the introduction of phosphonate moieties onto the aryl rings of **13.1** and **14.1**, and the reverse is also true.

10 Interconversions of the phosphonates between R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

The schemes above describe the preparation of phosphonates of general structure R-link-P(O)(OR¹)₂ in which the R¹ groups are defined as indicated in Chart 2, and the R group refers to the scaffold. The R¹ groups attached to the phosphonate esters in Chart 2 may be changed using established chemical transformations. The interconversion reactions of the phosphonates attached through the link group to the scaffold (R) are illustrated in Scheme 16. The interconversions may be carried out in the precursor compounds or the final products using the methods described below. The methods employed for a given phosphonate

transformation depend on the nature of the substituent R^1 . The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Macir, eds, Wiley, 1976, p. 9ff.

5 The conversion of a phosphonate diester 16.1 into the corresponding phosphonate monoester 16.2 (Scheme 16, Reaction 1) can be accomplished by a number of methods. For example, the ester 16.1 in which R^1 is an aralkyl group such as benzyl, can be converted into the monoester compound 16.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the
10 diester 16.1 in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 16.2 can be effected by treatment of the ester 16.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

Phosphonate diesters 16.2 in which one of the groups R^1 is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 16.2 in which R^1 is alkyl by hydrogenation,
15 for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester 16.2 in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl
20 carboxylates.

The conversion of a phosphonate diester 16.1 or a phosphonate monoester 16.2 into the corresponding phosphonic acid 16.3 (Scheme 16, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example,
25 dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 16.2 in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid 16.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester 16.2 in which R^1 is alkenyl such as,
30 for example, allyl, can be converted into the phosphonic acid 16.3 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous

ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985.

Palladium catalyzed hydrogenolysis of phosphonate esters **16.1** in which R^1 is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **16.1** in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.

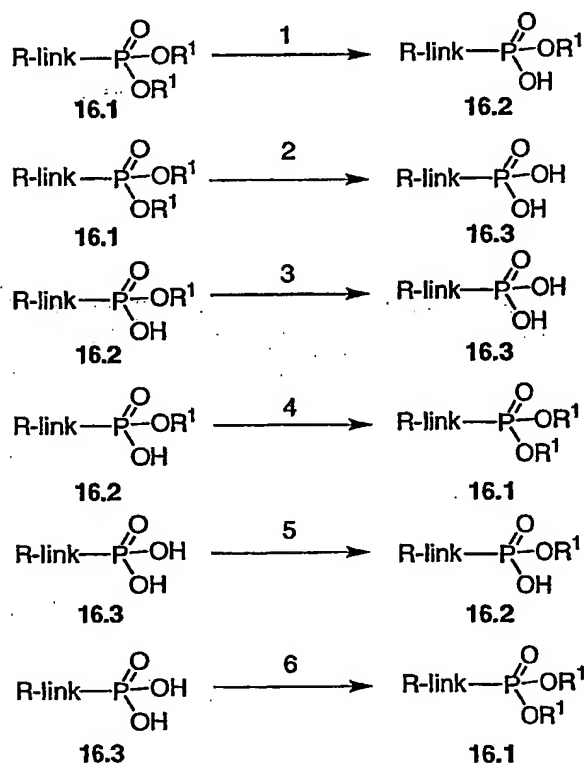
- 5 The conversion of a phosphonate monoester **16.2** into a phosphonate diester **16.1** (Scheme 16, Reaction 4) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **16.2** is reacted with a hydroxy compound R^1OH , in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a
- 10 carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the
- 15 reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine.. Alternatively, the conversion of the phosphonate monoester **16.1** to the diester **16.1** can be effected by the use of the Mitsunobu reaction. The substrate is reacted with the hydroxy compound R^1OH , in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **16.2**
- 20 can be transformed into the phosphonate diester **16.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br , in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate.
- Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a
- 25 two step procedure. In the first step, the phosphonate monoester **16.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in *Organic Phosphorus Compounds*, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate
- 30 diester **16.1**.

A phosphonic acid R-link-P(O)(OH)₂ can be transformed into a phosphonate monoester RP(O)(OR¹)(OH) (Scheme 16, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester R-link-P(O)(OR¹)₂ 16.1, except that only one molar proportion of the component R¹OH or R¹Br is employed. A phosphonic acid R-link-

- 5 P(O)(OH)₂ 16.3 can be transformed into a phosphonate diester R-link-P(O)(OR¹)₂ 16.1 (Scheme 16, Reaction 6) by a coupling reaction with the hydroxy compound R¹OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids 16.3 can be transformed into phosphonic esters 16.1 in which R¹ is aryl, by means of a coupling
- 10 reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°. Alternatively, phosphonic acids 16.3 can be transformed into phosphonic esters 16.1 in which R¹ is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R¹Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester 16.1.

15

Scheme 16



Amprenavir-like phosphonate protease inhibitors (AMLPPD)**5 Preparation of the intermediate phosphonate esters 1-13.**

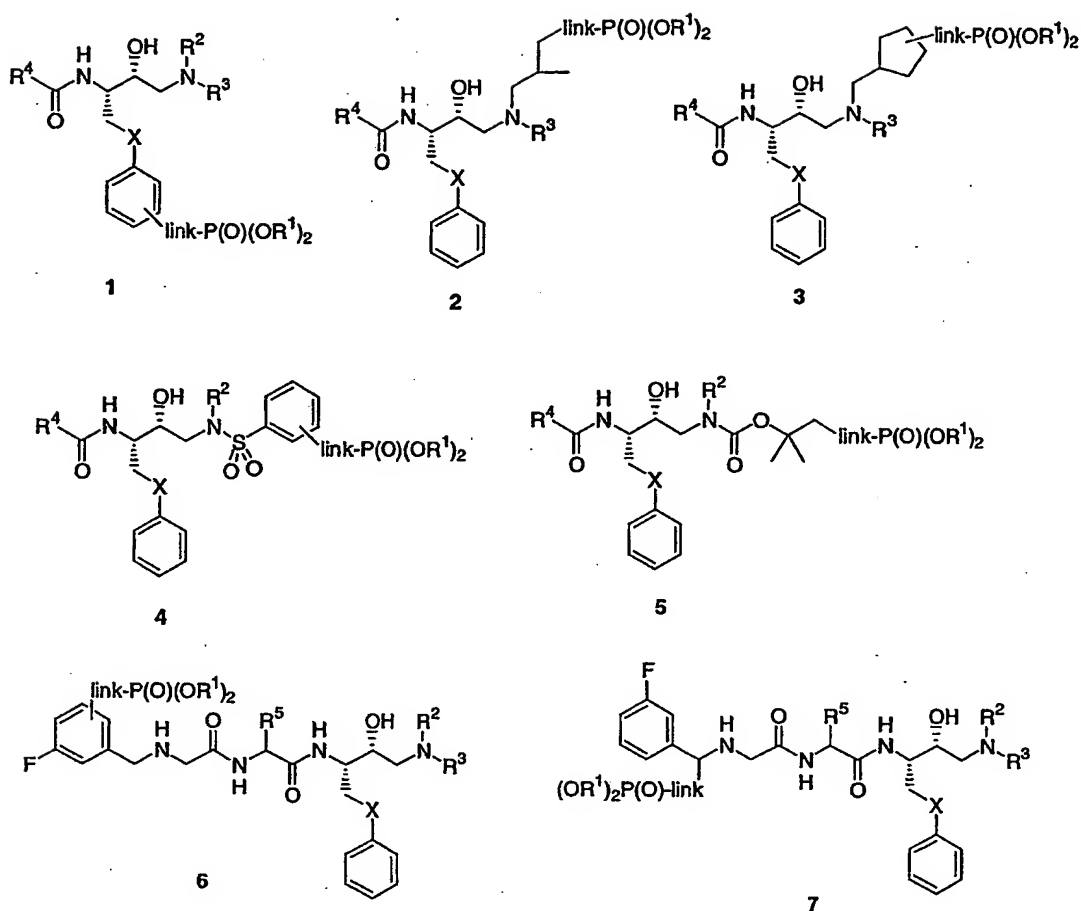
The structures of the intermediate phosphonate esters **1** to **13** and the structures of the component groups R^1 , R^5 , X of this invention are shown in Charts **1** - **2**. The structures of the R^2NH_2 components are shown in Chart **3**; the structures of the R^3-Cl components are shown
10 in Chart **4**; the structures of the R_4COOH groups are shown in Chart **5a-c**; and the structures of the $R^9CH_2NH_2$ amine components are illustrated in Chart **6**.

Specific stereoisomers of some of the structures are shown in Charts **1** - **6**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **13**. Subsequent chemical modifications to the compounds **1** to **10**, as described herein, permit the synthesis of the final
15 compounds of this invention.

The intermediate compounds **1** to **10** incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **7**, and **8** illustrate examples of the linking groups present in the structures **1** - **10**.

20 Schemes **1** - **99** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1** - **10**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **11**, **12** and **13**, in which a phosphonate moiety is incorporated into one of the groups R^4 , R^3 , R^2 , respectively, is also described below.

Chart 1

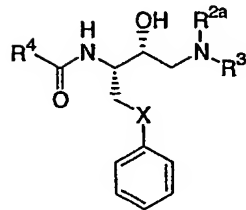
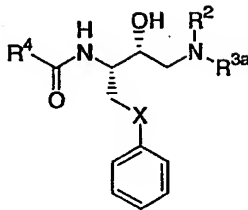
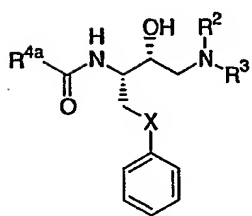
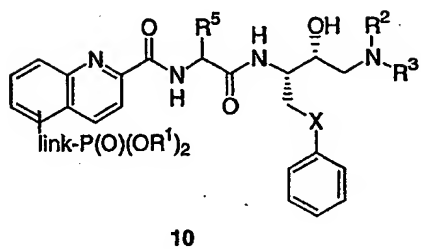
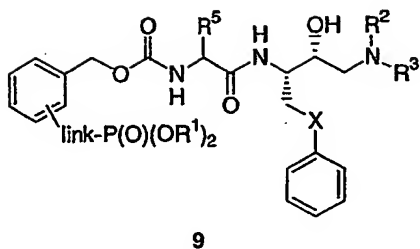
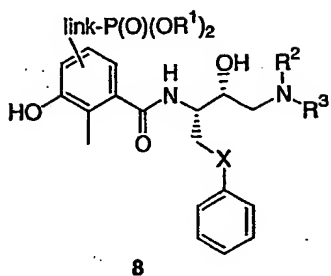


$R^1 = \text{H, alkyl, haloalkyl, alkenyl, aralkyl, aryl}$

$X = \text{S or direct bond}$

$R^5 = \text{alkyl, CH}_2\text{SO}_2\text{CH}_3, \text{C(CH}_3)_2\text{SO}_2\text{CH}_3, \text{CH}_2\text{CONH}_2, \text{CH}_2\text{SCH}_3, \text{imidaz-4-ylmethyl, CH}_2\text{NHAc, CH}_2\text{NHCOCF}_3, \text{tert-butyl}$

Chart 2



R^{4a} = phosphonate containing R^4 R^{3a} = phosphonate containing R^3 R^{2a} = phosphonate containing R^2

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

X = S or direct bond

R^5 = alkyl, $CH_2SO_2CH_3$, $C(CH_3)_2SO_2CH_3$, CH_2CONH_2 , CH_2SCH_3 , imidaz-4-ylmethyl, CH_2NHAc , $CH_2NHCOCF_3$, tert-butyl

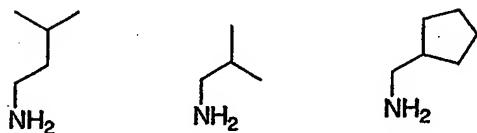
Chart 3 Structures containing the R²-NH₂ components**Chart 4 Structures containing the R³-Cl components**

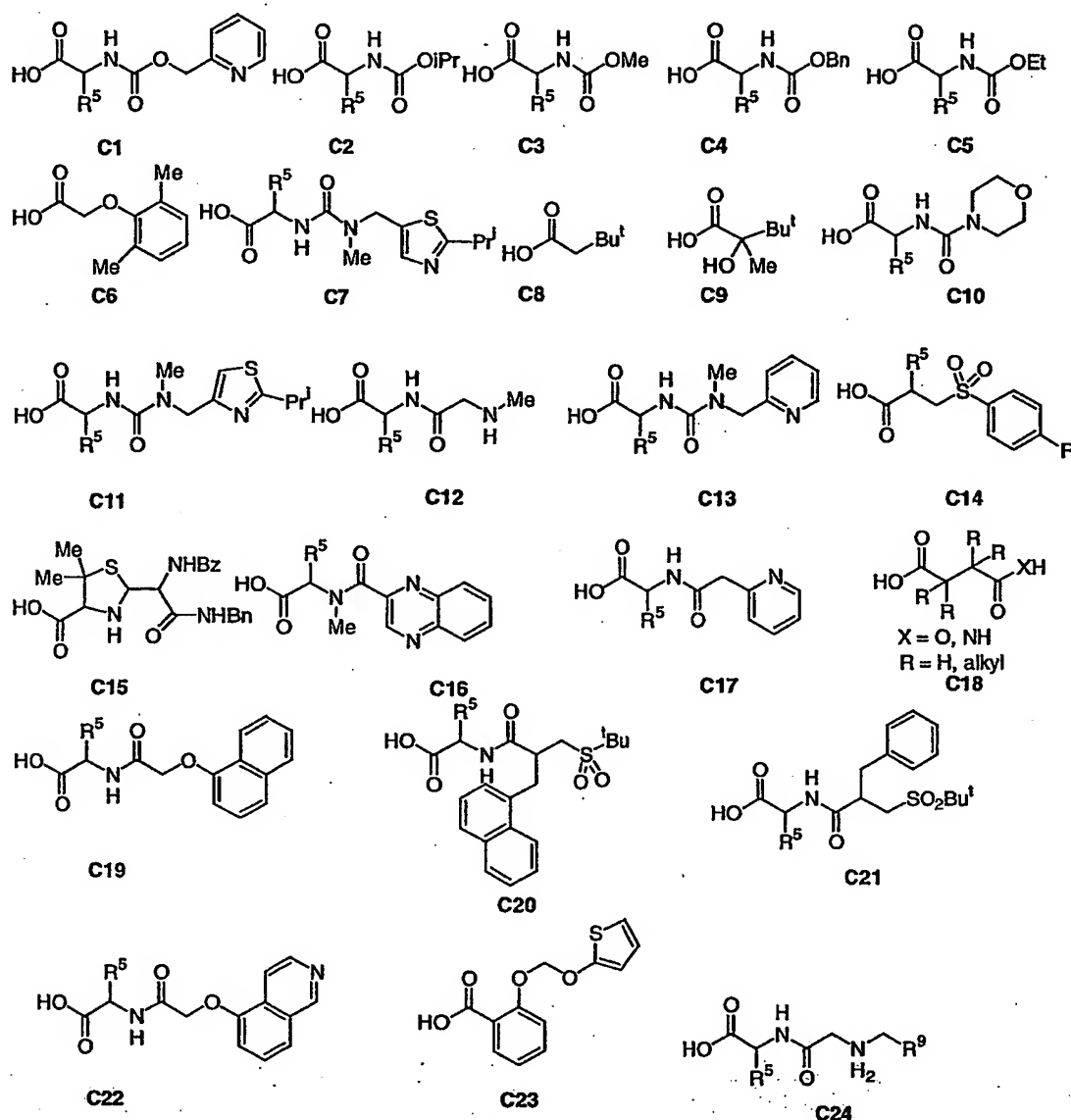
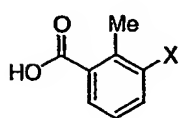
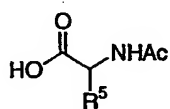
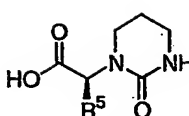
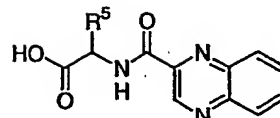
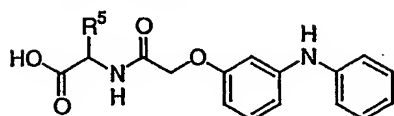
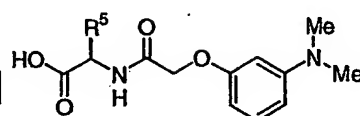
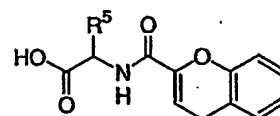
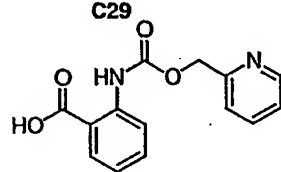
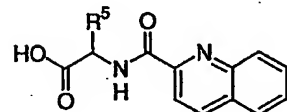
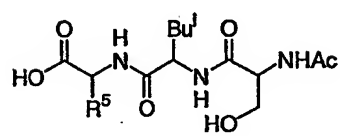
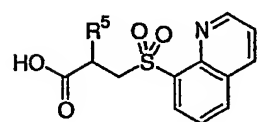
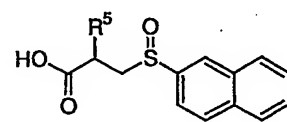
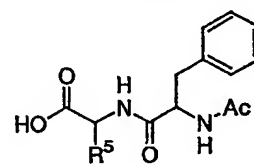
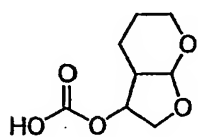
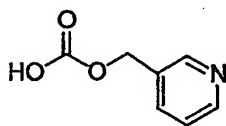
Chart 5a Structures of the R^4 COOH components

Chart 5b Structures of the R⁴COOH components**C25**X = OH, NH₂**C26****C27****C28****C29****C30****C31****C32****C33****C34****C35****C36****C37**

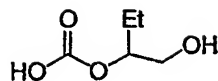
R⁵ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, Imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃, tert-butyl

Chart 5c Structures of the R⁴COOH components

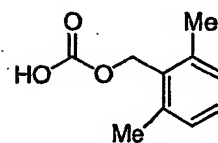
C38



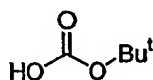
C39



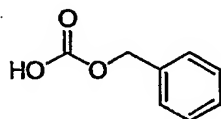
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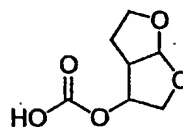
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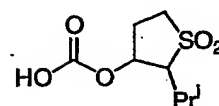
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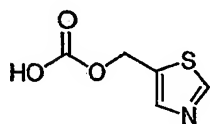
C43



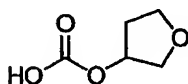
C44



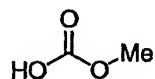
C45



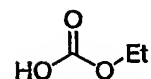
C46



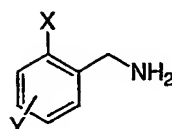
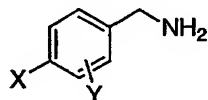
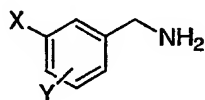
C47



C48



C49

Chart 6 Structures of the R⁹CH₂NH₂ components

X = F, Br, Cl ; Y = H, F, Br, Cl

Chart 7

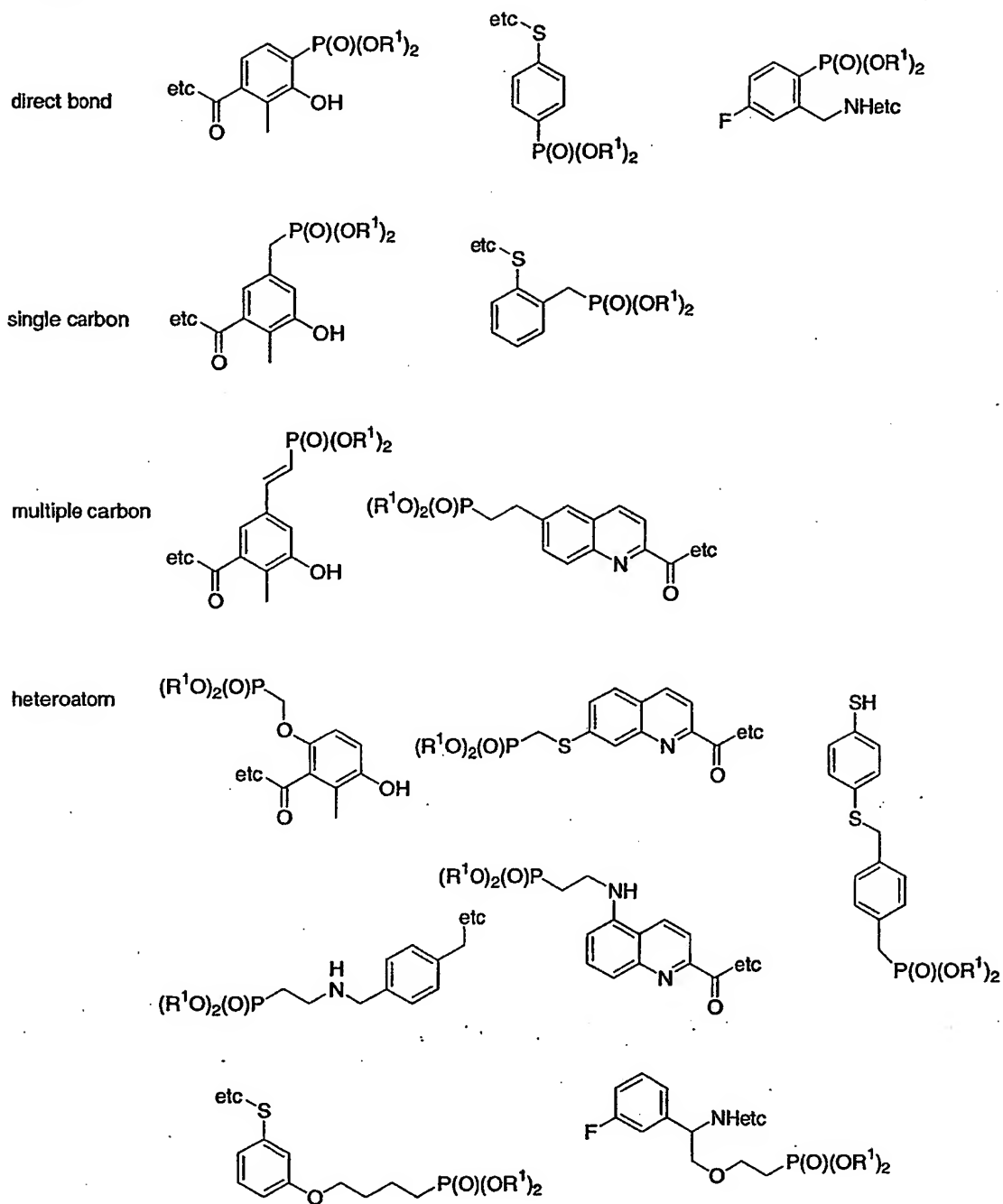
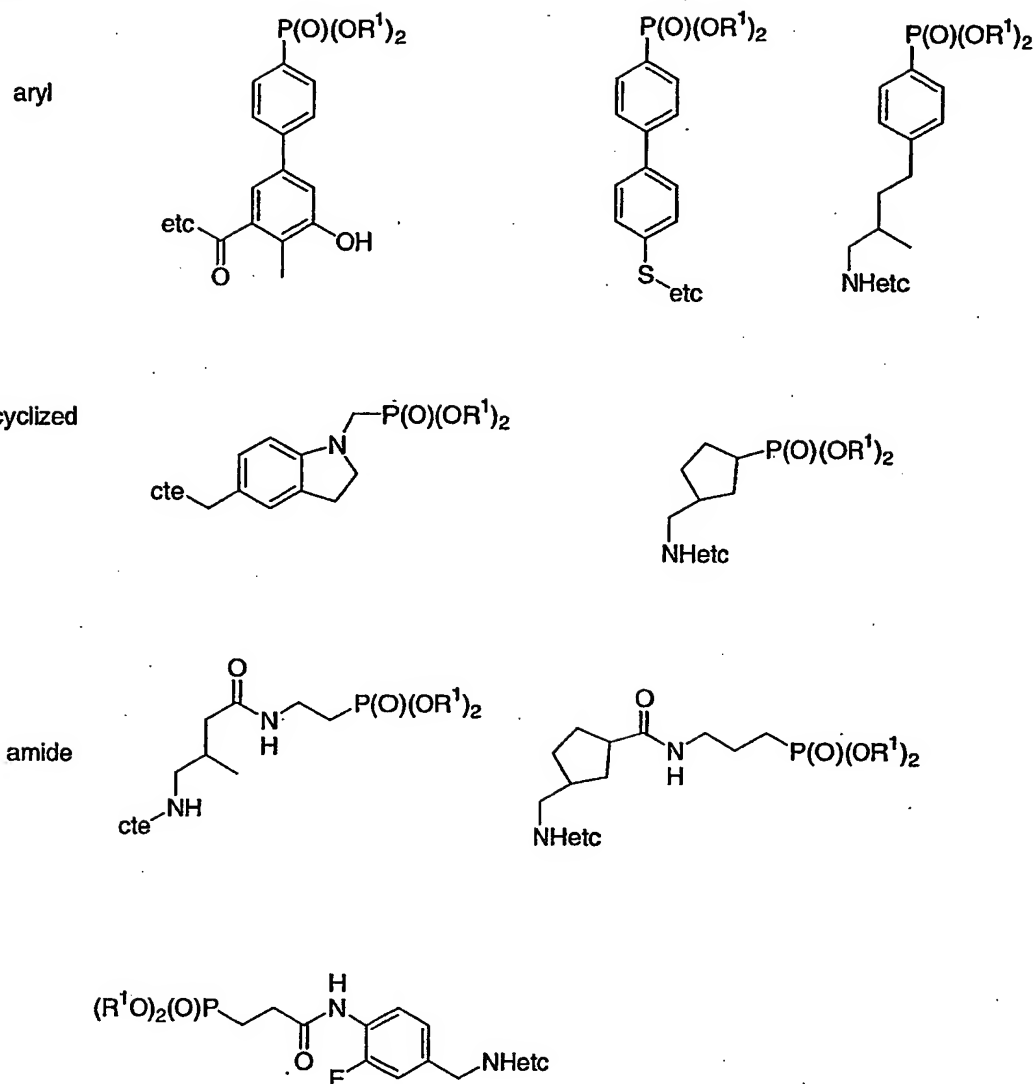


Chart 8



Protection of reactive substituents.

- 5 Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990
- 10 or Third Edition 1999. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], etc.

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

The intermediate phosphonate esters 1, in which the group A is attached to the aryl moiety, the $R_4\text{COOH}$ group does not contain an secondary amine, and in which the substituent A is either the group link- $\text{P}(\text{O})(\text{OR}^1)_2$ or a precursor such as $[\text{OH}]$, $[\text{SH}]$, $[\text{NH}]$, Br etc are prepared as shown in Schemes 1-2. The epoxide 1.1 in which the substituent A is either the group link- $\text{P}(\text{O})(\text{OR}^1)_2$ or a precursor such as $[\text{OH}]$, $[\text{SH}]$, $[\text{NH}]$, Br is prepared as described in Schemes 56-59 below. Treatment of the epoxide 1.1 with the amine 1.2 affords the aminoalcohol 1.3. The preparation of aminoalcohols by reaction between an amine and an epoxide is described, for example, in Advanced Organic Chemistry, by J. March, McGraw Hill, 1968, p 334. In a typical procedure, equimolar amounts of the reactants are combined in a polar solvent such as an alcohol or dimethylformamide and the like, at from ambient to about 100° , for from 1 to 24 hours, to afford the product 1.3. The amino alcohol 1.3 is then treated with an acylating agent 1.4 to afford the product 1.5. The acylating agent is typically a chloroformate or a sulfonyl chloride as shown in chart 4. Coupling conditions for amines with sulfonyl chlorides is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 603-615 or for chloroformates, p494ff. Preferably, the amine 1.3 is treated with the sulfonyl chloride 1.4 in the presence of a base such as pyridine, potassium carbonate etc and THF / water to give the product 1.5. Product 1.5 is deprotected using conditions described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 503ff. Preferably, the BOC amine is treated with TFA in an aprotic solvent such as THF. Conversion to the amide 1.8 is performed using standard coupling conditions between an acid 1.7 and the amine. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride or anhydride, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

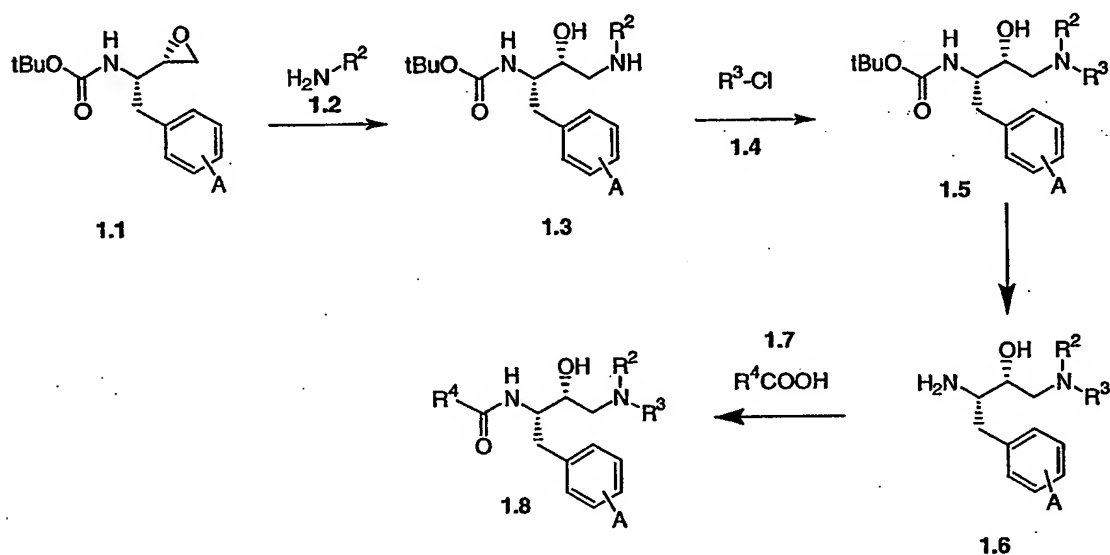
The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid 1.7 is reacted with an equimolar amount of the amine 1.6 in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, in an aprotic solvent such as, for example, tetrahydrofuran, at about ambient temperature, so as to afford the amide product 1.8. The compound 1.8, and analogous acylation products described below, in which the carboxylic acid R^4COOH is one of the carbonic acid derivatives C38-C49, as defined in Chart 5c, are carbamates. Methods for the preparation of carbamates are described below, Scheme 98.

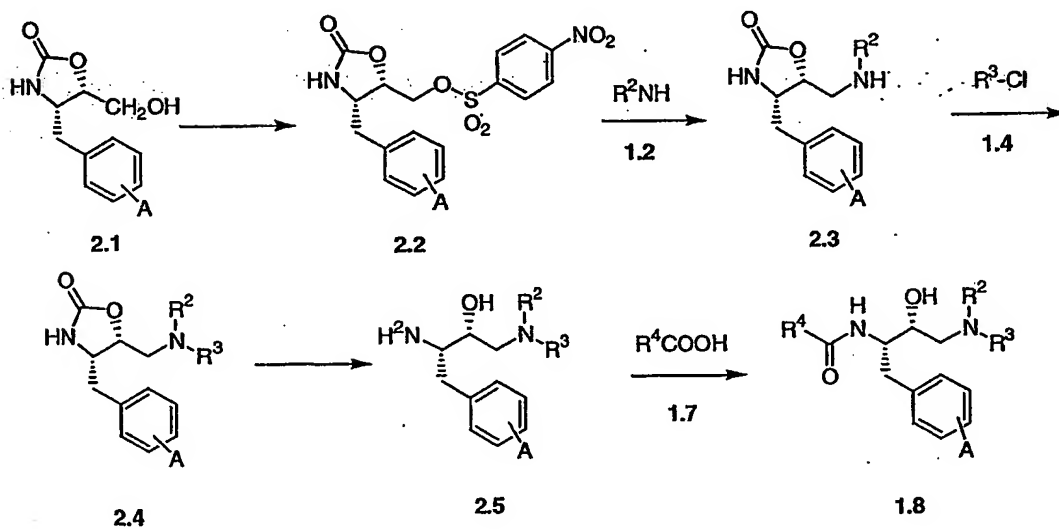
Scheme 2 illustrates an alternative method for the preparation of intermediate phosphonate esters 1, in which the group A is attached to the aryl moiety, the R_4COOH group does not contain an secondary amine, and in which the substituent A is either the group link-
P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. The oxazolidinone 2.1, prepared as described in Schemes 60-62, is first activated as shown in 2.2 and then treated with amine 1.2 to afford the secondary amine 2.3. The hydroxyl group can be activated by converting into a bromo derivative, for example by reaction with triphenylphosphine and carbon tetrabromide, as described in J. Am. Chem. Soc., 92, 2139, 1970, or a methanesulfonyloxy derivative, by reaction with methanesulfonyl chloride and a base, or, preferably, into the 4-nitrobenzenesulfonyloxy derivative 2.2, by reaction in a solvent such as ethyl acetate or tetrahydrofuran, with 4-nitrobenzenesulfonyl chloride and a base such as triethylamine or N-methylmorpholine, as described in WO 9607642. The nosylate product 2.2 is then reacted with the amine component 1.2 to afford the displacement product 2.3. Equimolar amounts of the reactants are combined in an inert solvent such as dimethylformamide, acetonitrile or acetone, optionally in the presence of an organic or inorganic base such as triethylamine or sodium carbonate, at from about 0°C to 100°C to afford the amine product 2.3. Preferably, the reaction is performed in methyl isobutyl ketone at 80°C, in the presence of sodium carbonate, as described in WO 9607642. Treatment of the amine product 2.3 with the R3 chloride 1.4 as described in Scheme 1 then affords the product 2.4. The oxazolidinone group present in the product 2.4 is then hydrolyzed to afford the hydroxyamine 2.5. The hydrolysis reaction is effected in the presence of aqueous solution of a

- base such as an alkali metal hydroxide, optionally in the presence of an organic co-solvent. Preferably, the oxazolidinone compound 2.4 is reacted with aqueous ethanolic sodium hydroxide at reflux temperature, as described in WO 9607642, to afford the amine 2.5. This product is then reacted with the $R^4\text{COOH}$ carboxylic acid or activated derivative thereof, 1.7, to afford the product 1.8. The amide-forming reaction is conducted under the same conditions as described above, (Scheme 1).

Scheme 1



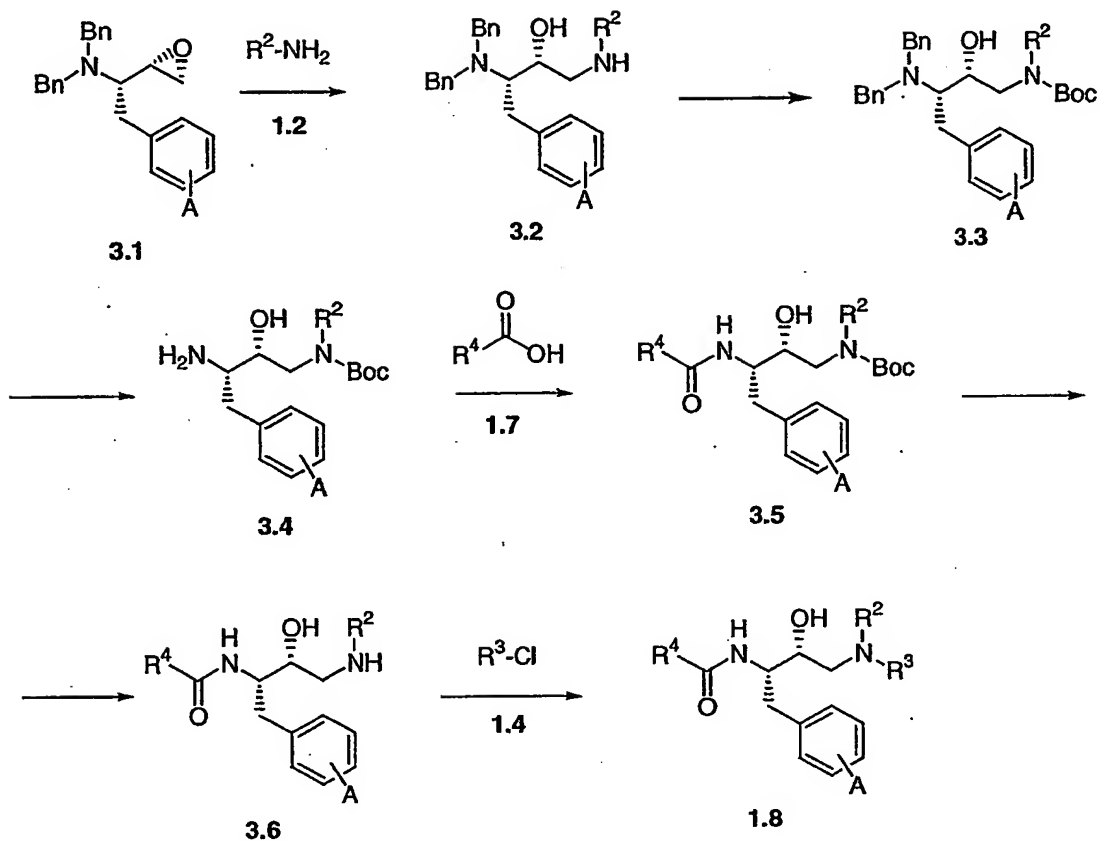
Scheme 2



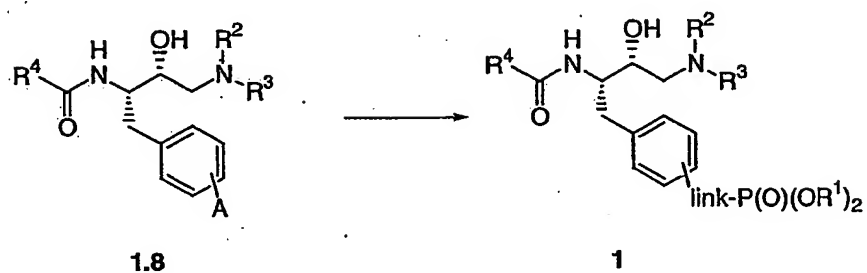
Scheme 3 illustrates the preparation of intermediate phosphonate esters 1, in which the group A is attached to the aryl moiety, the R_4COOH group contains an secondary amine, and in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. The dibenzyl amine 3.2 is prepared from epoxide 3.1 and amine 1.2 ,
5 following the same procedures described in Scheme 1 for the preparation of 1.3. Epoxide 3.1 is prepared as described below in Schemes 56a. The amine 3.2 is then converted to the amine 3.4 as described in US6391919. Preferably, the amine is first protected as the BOC carbamate and then treated with palladium hydroxide on carbon (20%) in methanol under hydrogen at high pressure to give the amine 3.4. Treatment of 3.4 with the R_4COOH acid 1.7 which
10 contains a secondary or primary amine, under standard amide bond forming conditions as described above, Scheme 1, then affords the amide 3.5. Preferably, the acid 1.7, EDC and *n*-hydroxybenzotriazole in DMF is treated with the amine 3.4 to give the amide 3.5. Removal of the BOC group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 520-525 then affords the amine 3.6. Preferably
15 the BOC amine 3.5 is treated with HCl in dioxane and water to give the free amine 3.6. The amine 3.6 is then treated with an acylating agent such as an acid, chloroformate or sulfonyl chloride to give the final product 1.8. Standard coupling conditions for amines with acids or sulfonyl chlorides is indicated above Scheme 1. Preferably, the amine 3.6 is treated with nitro-sulfonyl chloride in THF and water in the presence of a base such as potassium carbonate
20 to give the sulfonamide 1.8.

The reactions shown in Scheme 1-3 illustrate the preparation of the compound 1.8 in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 4 depicts the conversion of 1.8 in which A is [OH], [SH], [NH], Br etc,
25 into the phosphonate ester 1 in which X is a direct bond. In this procedure 1.8 is converted, using the procedures described below, Schemes 47-99, into the compound 1. Also, in the preceding and following Schemes, the amino substituted sulfonamide reagents are typically introduced as a nitro-sulfonamide reagents. Therefore, where appropriate, an additional step of nitro group reduction as described in Comprehensive Organic Transformations, by R. C.
30 Larock, 2nd Edition, 1999, p.821ff, is performed to give the final amino products.

Scheme 3



Scheme 4



Scheme 5 illustrates an alternative method for the preparation of the compound 1 in which the group A is attached to the aryl moiety, the R_4COOH group contains a primary or secondary amine and in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. The amine 3.4, (Scheme 3) is treated with an amino acid 5.1

under typical amide bond forming conditions to give the amide 5.2 as described above, Scheme 1. Preferably the acid 5.1 is first treated with EDC and n-hydroxybenzotriazole in DMF and then the amine 3.4 is added in DMF followed by N-methyl morpholine to give the amide 5.2. Reduction of the amide under the same catalytic hydrogenation conditions as described above in Scheme 3 gives the free amine 5.3. The amine is further treated with chloroacetyl chloride to provide the chloro compound 5.4. Preferably treatment with the chloroacetyl chloride is performed in ethyl acetate and water mixture in the presence of a base such as potassium hydrogen carbonate. The chloro compound 5.4 is treated with hydrochloric acid in dioxane and ethyl acetate to give the salt of the free amine 5.5. The salt 5.5 is then treated with a nitro-sulfonyl chloride 1.4 in THF and water in the presence of a base such as potassium carbonate to give the sulfonamide 5.6. Alternatively the free amine 5.5 is treated with a chloroformate 1.4 in the presence of a base such as triethylamine to afford the carbamate. Methods for the preparation of carbamates are also described below, Scheme 98. Compound 5.6 is then treated with the amine 5.7 to give the secondary amine 5.8. Preferably the chloride is refluxed in the presence of the amine 5.7 in THF.

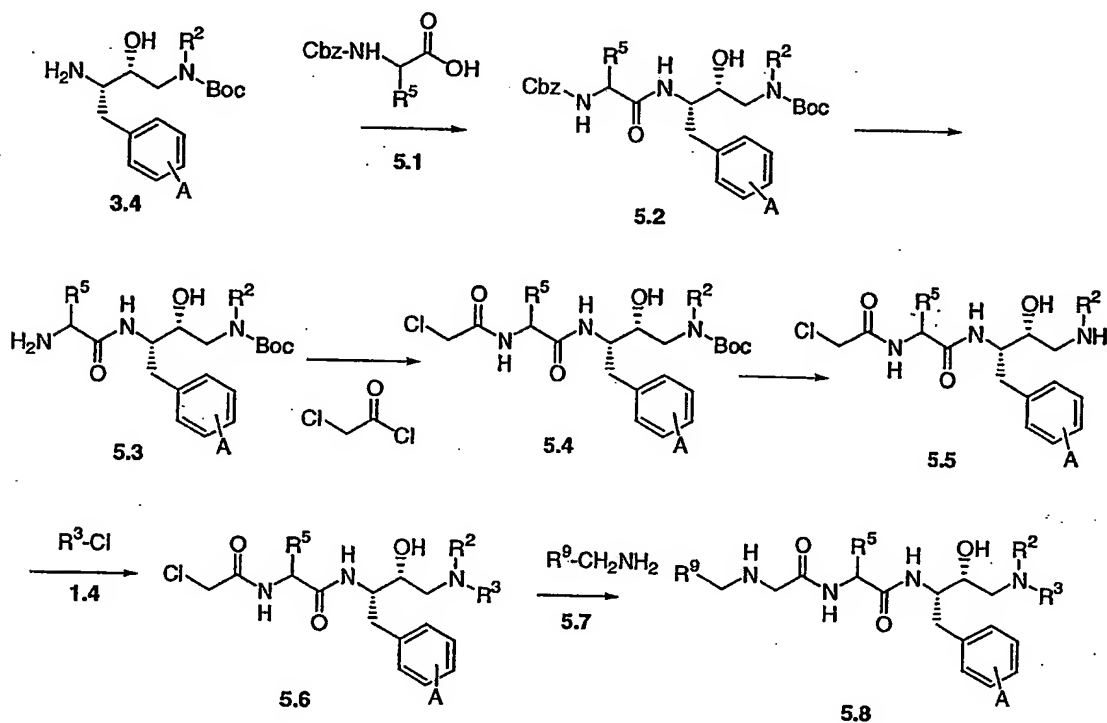
The reactions shown in Scheme 5 illustrate the preparation of the compound 5.8 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 6 depicts the conversion of 5.8 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 1 in which X is a direct bond. In this procedure 5.8 is converted, using the procedures described below, Schemes 47-99, into the compound 1.

In the preceding and following schemes, the conversion of various substituents into the group $\text{link-P(O)(OR}^1)_2$ can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, during the introduction of the group $\text{link-P(O)(OR}^1)_2$.

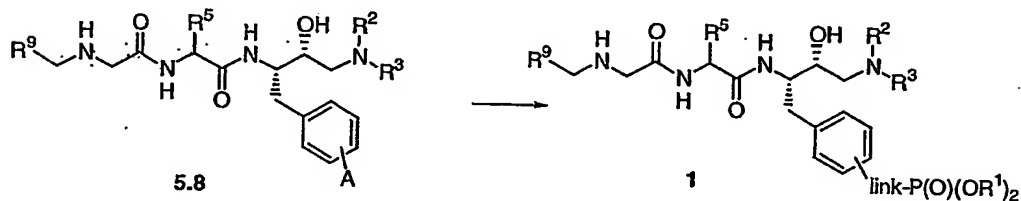
In the preceding and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical

transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 99).

Scheme 5



Scheme 6



5

Preparation of the phosphonate ester intermediates 1 in which X is a sulfur.

The intermediate phosphonate esters 1, in which X is sulfur, the R₄COOH group does not contain a amine group, and in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, are prepared as shown in Schemes 7-9.

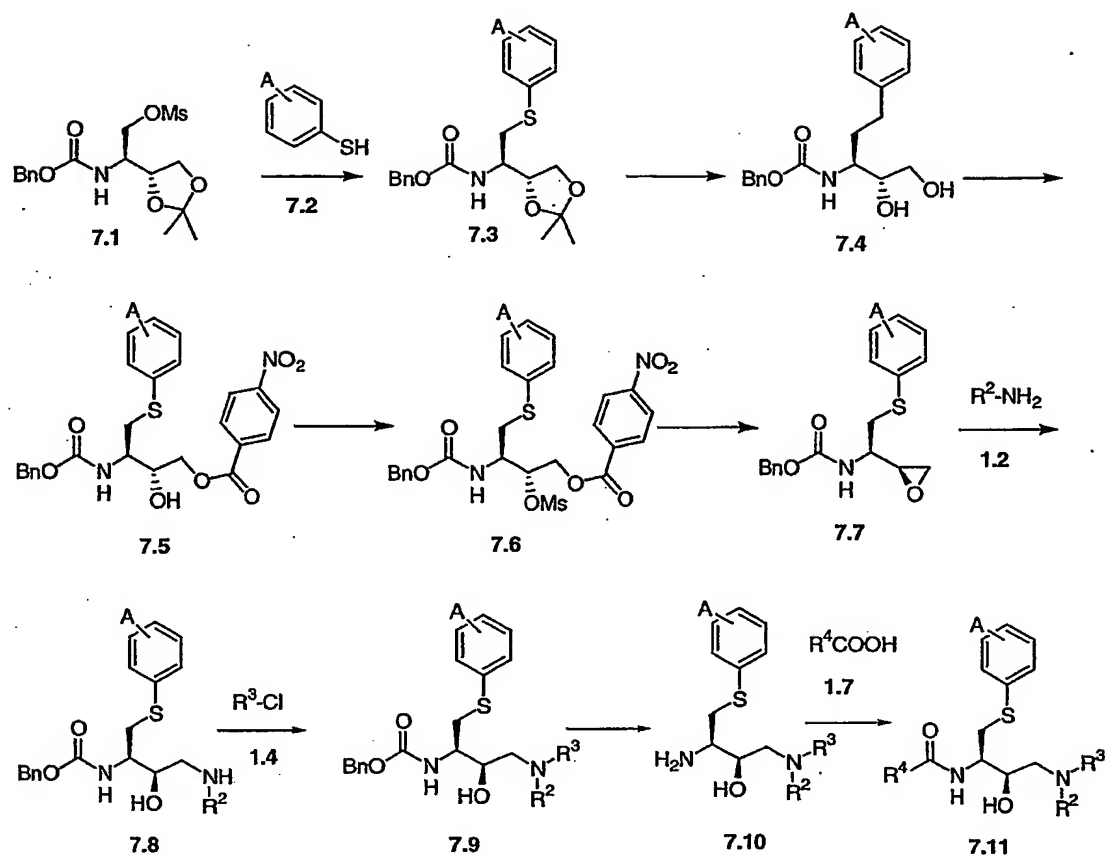
10

Scheme 7 illustrates one method for the preparation of the compounds 1 in which the substituent X is S, and in which the group A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor thereto, such as [OH], [SH] Br etc. In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, 7.1, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol 7.2 to afford the thioether 7.3. The preparation of thiol 7.2 is described in Schemes 63-72. The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the like, in the presence of an inorganic or organic base, at from 0°C to 80°C, for from 1-12 hours, to afford the thioether 7.3. Preferably the mesylate 7.1 is reacted with an equimolar amount of the thiol, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°C, to give the product 7.3. The 1,3-dioxolane protecting group present in the compound 7.3 is then removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol 7.4. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p191. For example, the 1,3-dioxolane compound 7.3 is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane 7.3 is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°C, to yield the product 7.4. The primary hydroxyl group of the diol 7.4 is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as dichloromethane and the like, in the presence of an inorganic or organic base. Preferably, equimolar amounts of the diol 7.4 and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the hydroxy ester 7.5. The hydroxy ester is next reacted with a sulfonyl chloride such as methanesulfonyl chloride, 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the corresponding sulfonyl ester 7.6. Preferably, equimolar amounts of the carbinol 7.5 and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the mesylate 7.6. The compound 7.6 is then subjected to a hydrolysis-

cyclization reaction to afford the oxirane 7.7. The mesylate or analogous leaving group present in 7.6 is displaced by hydroxide ion, and the carbinol thus produced, without isolation, spontaneously transforms into the oxirane 7.7 with elimination of 4-nitrobenzoate. To effect this transformation, the sulfonyl ester 7.6 is reacted with an alkali metal hydroxide or
5 tetraalkylammonium hydroxide in an aqueous organic solvent. Preferably, the mesylate 7.6 is reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour, to afford the oxirane 7.7.

The oxirane compound 7.7 is then subjected to regiospecific ring-opening reaction by treatment with a secondary amine 1.2, to give the aminoalcohol 7.8. The amine and the
10 oxirane are reacted in a protic organic solvent, optionally in the additional presence of water, at 0°C to 100°C, and in the presence of an inorganic base, for 1 to 12 hours, to give the product 7.8. Preferably, equimolar amounts of the reactants 7.7 and 1.2 are reacted in aqueous methanol at about 60°C in the presence of potassium carbonate, for about 6 hours, to afford the aminoalcohol 7.8. The free amine is then substituted by treatment with an acid,
15 chloroformate or sulfonyl chloride as described above in Scheme 1 to give the amine 7.9. The carbobenzyloxy (cbz) protecting group in the product 7.9 is removed to afford the free amine 7.10. Methods for removal of cbz groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition, p. 335. The methods include catalytic hydrogenation and acidic or basic hydrolysis. For example, the cbz-protected
20 amine 7.9 is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or alcoholic solvent, to yield the free amine 7.10. Preferably, the cbz group is removed by the reaction of 7.9 with potassium hydroxide in an alcohol such as isopropanol at ca. 60°C to afford the amine 7.10. The amine 7.10 so obtained is next acylated with a carboxylic acid or activated derivative 1.7, using the conditions described above in Scheme 1 to afford the
25 product 7.11

Scheme 7



Scheme 8 illustrates an alternative preparation of the compounds 1 in which the substituent X is S, and in which the group A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br etc. In this sequence, 4-amino-tetrahydro-furan-3-ol, 8.1, the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with a carboxylic acid or activated derivative thereof, R⁴COOH, 1.7, using the conditions described above for in Scheme 1 for the preparation of amides, to afford the amide 8.2. The amide product 8.2 is then transformed, using the sequence of reactions shown in Scheme 8, into the isoxazoline compound 8.5. The hydroxyl group on the tetrahydrofuran moiety in 8.2 is converted into a leaving group such as p-toluenesulfonyl or the like, by reaction with a sulfonyl chloride in an aprotic solvent such as pyridine or dichloromethane. Preferably, the hydroxy amide 8.2 is reacted with an equimolar amount of methanesulfonyl chloride in pyridine, at ambient temperature, to afford the methanesulfonyl ester 8.3. The product 8.3, bearing a suitable sulfonyl ester leaving group, is then subjected to acid-catalyzed rearrangement to afford the isoxazoline 8.4. The

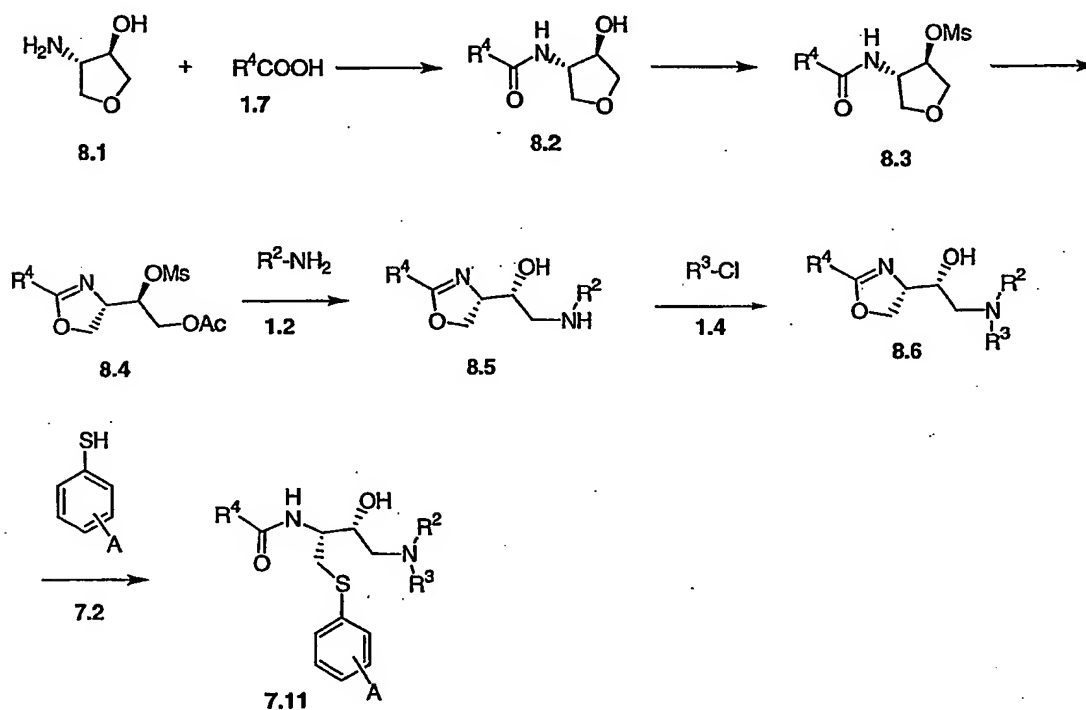
rearrangement reaction is conducted in the presence of an acylating agent such as a carboxylic anhydride, in the presence of a strong acid catalyst. Preferably, the mesylate 8.3 is dissolved in an acylating agent such as acetic anhydride at about 0°C, in the presence of about 5 mole % of a strong acid such as sulfuric acid, to afford the isoxazoline mesylate 8.4. The leaving group, for example a mesylate group, is next subjected to a displacement reaction with an amine. The compound 8.4 is reacted with an amine 1.2, as defined in Chart 3, in a protic solvent such as an alcohol, in the presence of an organic or inorganic base, to yield the displacement product 8.5. Preferably, the mesylate compound 8.4 is reacted with an equimolar amount of the amine 1.2, in the presence of an excess of an inorganic base such as potassium carbonate, at ambient temperature, to afford the product 8.5. The product 8.5 is then treated with R^3Cl , chart 6 as described above in Scheme 1 to afford the amine 8.6. The compound 8.6 is then reacted with a thiol 7.2 to afford the thioether 7.11. The reaction is conducted in a polar solvent such as DMF, pyridine or an alcohol, in the presence of a weak organic or inorganic base, to afford the product 7.11. Preferably, the isoxazoline 8.6 is reacted, in methanol, with an equimolar amount of the thiol 7.2, in the presence of an excess of a base such as potassium bicarbonate, at ambient temperature, to afford the thioether 7.11.

The procedures illustrated in Scheme 7-8 depict the preparation of the compounds 7.11 in which X is S, and in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br etc, as described below. Scheme 9 illustrates the conversion of compounds 7.11 in which A is a precursor to the group $\text{link-P(O)(OR}^1)_2$ into the compounds 1 in which $X=S$. Procedures for the conversion of the substituent A into the group $\text{link-P(O)(OR}^1)_2$ are illustrated below, (Schemes 47 - 99).

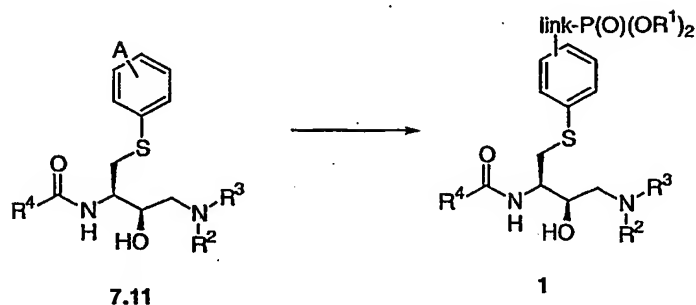
Scheme 9a-9b depicts the preparation of phosphonate esters 1, in which X is sulfur, the R_4COOH group does contain a amine group, and in which substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. The amine 7.10 prepared in Scheme 7 is treated with the CBZ protected amine 5.1 using the same conditions described in Scheme 5 for the preparation of 5.2 to give CBZ amine 9a.1. Removal of the CBZ group as described in Scheme 5 to give 9a.2 followed by treatment with chloroacetyl chloride as described in Scheme 5 gives chloride 9a.3. The chloride 9a.3 is then treated with the amine 5.7 to give the amine 9a.4 as described in Scheme 5.

The reactions shown in Scheme 9a illustrate the preparation of the compound 9a.4 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 9b depicts the conversion of 9a.4 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 1 in which X is sulfur. In this procedure 9a.4 is converted, using the procedures described below, Schemes 47-99, into the compound 1.

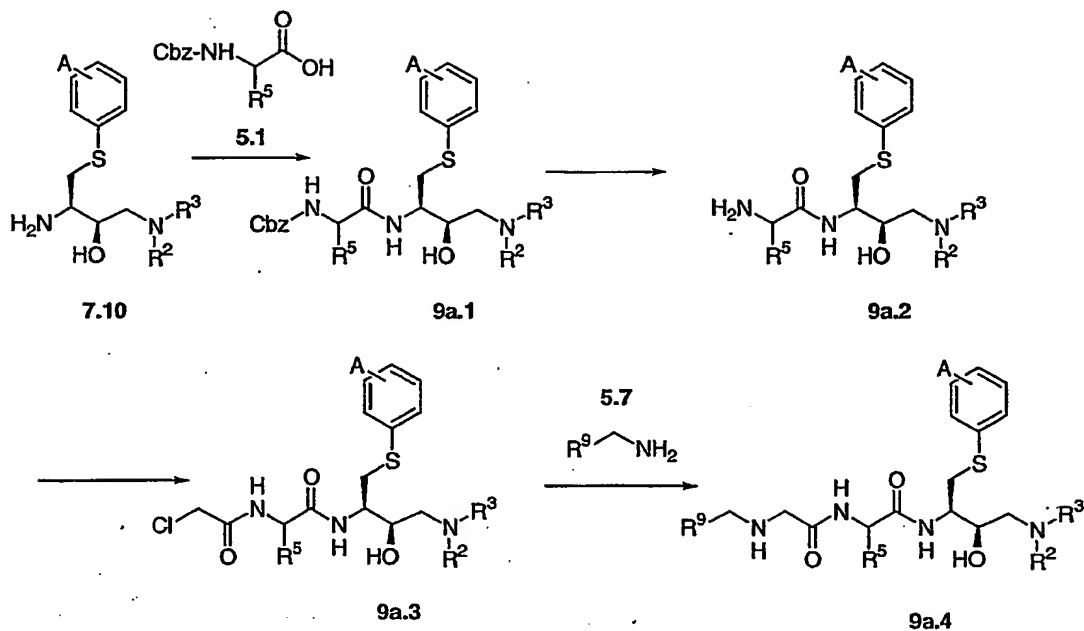
Scheme 8



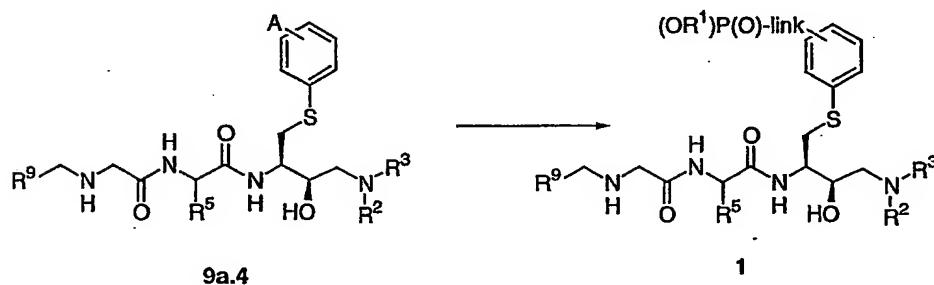
Scheme 9



Scheme 9a



Scheme 9b



Preparation of the phosphonate ester intermediates 2 and 3 in which X is a direct bond

5

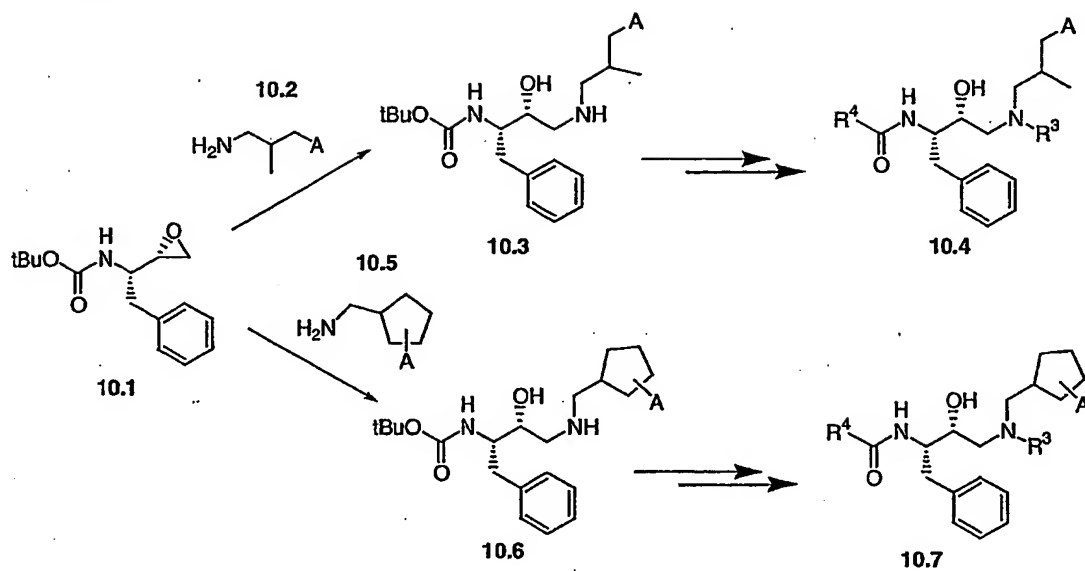
Schemes 10-12 illustrate the preparation of the phosphonate esters 2 and 3 in which X is a direct bond and the $R_4\text{COOH}$ group does not contain a primary or secondary amine group. As shown in Scheme 10, the epoxide 10.1, prepared as described in J. Med. Chem 1994, 37, 1758 is reacted with the amine 10.2 or 10.5, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, to afford the amine 10.3 and 10.6 respectively. The reaction is performed under the same conditions as described

above, Scheme 1 for the preparation of the amine 1.3. The preparation of the amines 10.2 is described in Schemes 73-75 and amines 10.5 in schemes 76-78. The products 10.3 and 10.6 are then transformed, using the sequence of reactions described above, Scheme 1, for the conversion of the amine 1.3 into the amide 1.8, into the aminoamide 10.4 and 10.7 respectively.

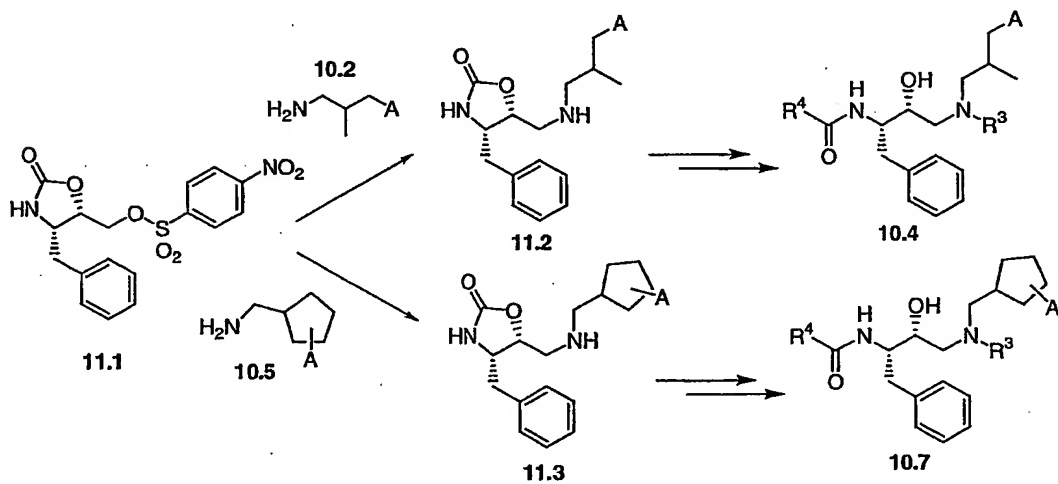
An alternative route to the amines 10.4 and 10.7 is shown in Scheme 11 in which sulfonyl ester 11.1 prepared according to Chimia 1996, 50, 532 is treated under conditions described in Scheme 2 with the amines 10.2 or 10.5 to give the amines 11.2 or 11.3 respectively. These amine products are then converted as described above, Scheme 2, into the amides 10.4 and 10.7 respectively.

The reactions shown in Scheme 10 and 11 illustrate the preparation of the compounds 10.4 and 10.7 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 12 depicts the conversion of these compounds 10.4 and 10.7 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 2 and 3 respectively, in which X is a direct bond. In this procedure, the amines 10.4 and 10.7 are converted, using the procedures described below, Schemes 47-99, into the compounds 2 and 3 respectively.

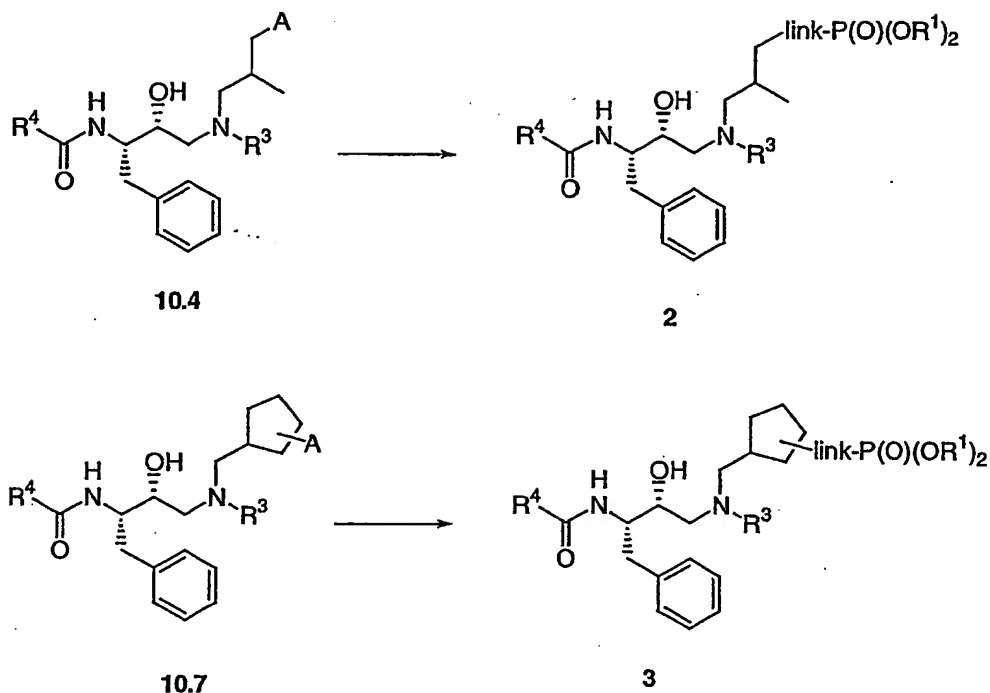
Scheme 10



Scheme 11



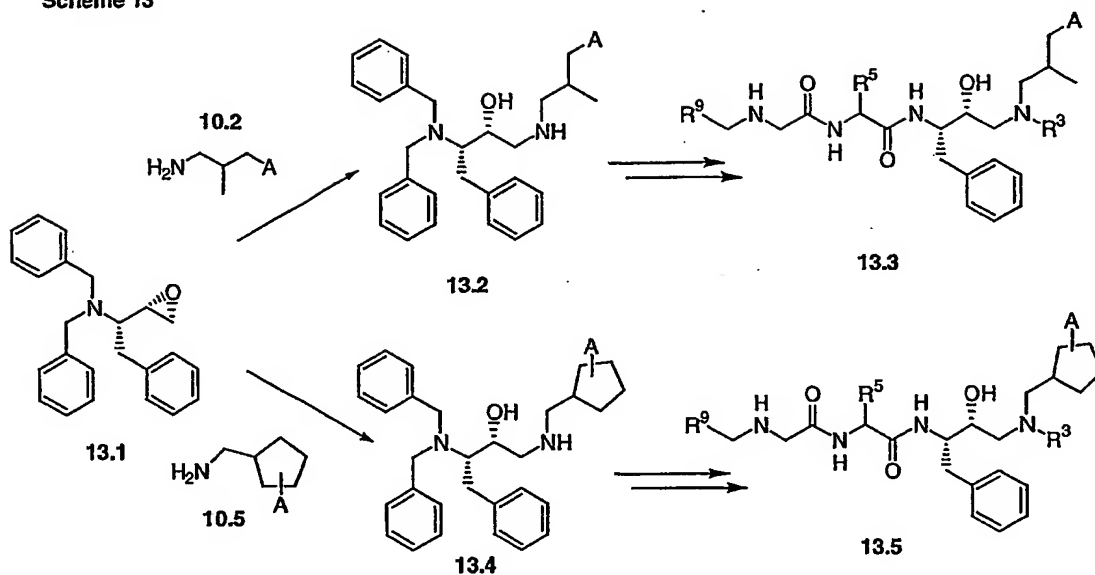
Scheme 12



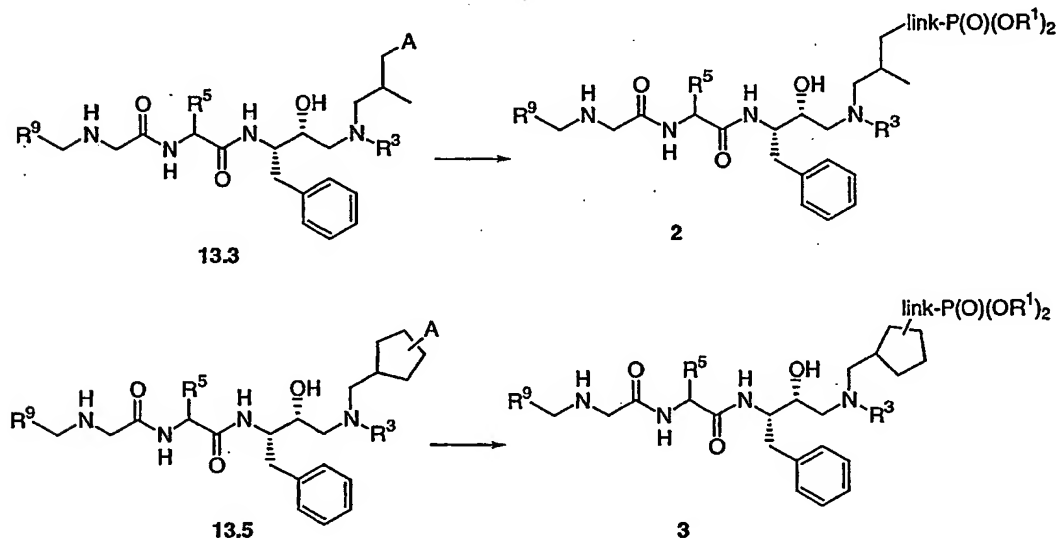
Schemes 13-14 illustrates the preparation of the phosphonate esters **2** and **3** in which X is a direct bond and the R_4COOH group contains an amine. The epoxide **13.1**, prepared as described in US 6391919B1, or J. Org. Chem. 1996, 61, 3635 is reacted, as described above, (Scheme 1) with the amine **10.2** or **10.5**, in which substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, to give the amino alcohols **13.2** and **13.4**, respectively. These amines are then converted as described in Scheme 3 for the conversion of **3.2** into **3.4** and Scheme 5 for the conversion of **3.4** into **5.8**, into the amine products **13.3** and **13.5** respectively.

The reactions shown in Scheme 13 illustrate the preparation of the compounds **13.3** and **13.5** in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 14 depicts the conversion of the compounds **13.3** and **13.5** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **2** and **3** in which X is a direct bond. In this procedure, the compounds **13.3** and **13.5** are converted, using the procedures described below, Schemes 47-99, into the compounds **2** and **3** respectively.

Scheme 13



Scheme 14

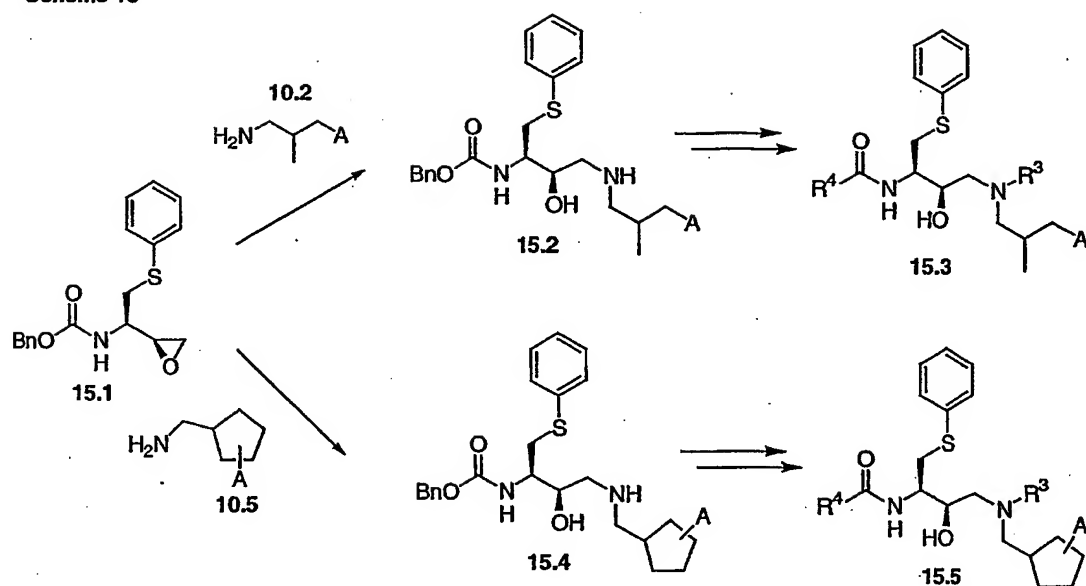


Preparation of the phosphonate ester intermediates 2 and 3 in which X is a sulfur

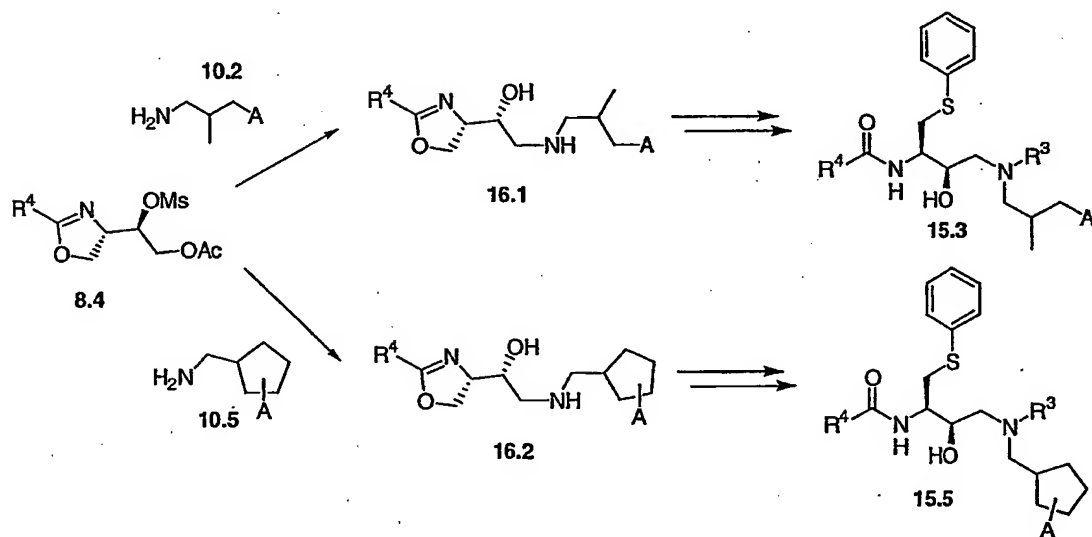
- 5 The intermediate phosphonate esters 2 and 3, in which the group A is attached to a sulfur linked aryl moiety, and the $R_4\text{COOH}$ group does not contain an amine group, are prepared as shown in Schemes 15-17. In Scheme 15, epoxide 15.1 is prepared from mesylate 7.1 using the conditions described in Scheme 7 for the preparation of 7.7 from 7.1, except incorporating

- thiophenol for thiol 7.2. The epoxide 15.1 is then treated with amine 10.2 or amine 10.5, in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme 7, to give the amines 15.2 and 15.4. Further application of Scheme 7 on the amines 15.2 and 15.4 yields the alcohols 15.3 and 15.5 respectively.
- 5 Alternatively, Scheme 16 depicts the preparation of 15.3 and 15.5 using the mesylate 8.4. The amines 10.2 and 10.5 are reacted with mesylate 8.4 under conditions described in Scheme 8 to give amines 16.1 and 16.2 respectively. Further modification of 16.1 and 16.2 according to the conditions described in Scheme 8 then affords alcohols 15.3 and 15.5 respectively.
- 10 The reactions shown in Scheme 15-16 illustrate the preparation of the compounds 15.3 and 15.5 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 17 depicts the conversion of 15.3 and 15.5 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 2 and 3 in which X is sulfur. In this procedure 15.3 or 15.5 is converted, using the procedures described below, Schemes 47-99,
- 15 into the compound 2 and 3.

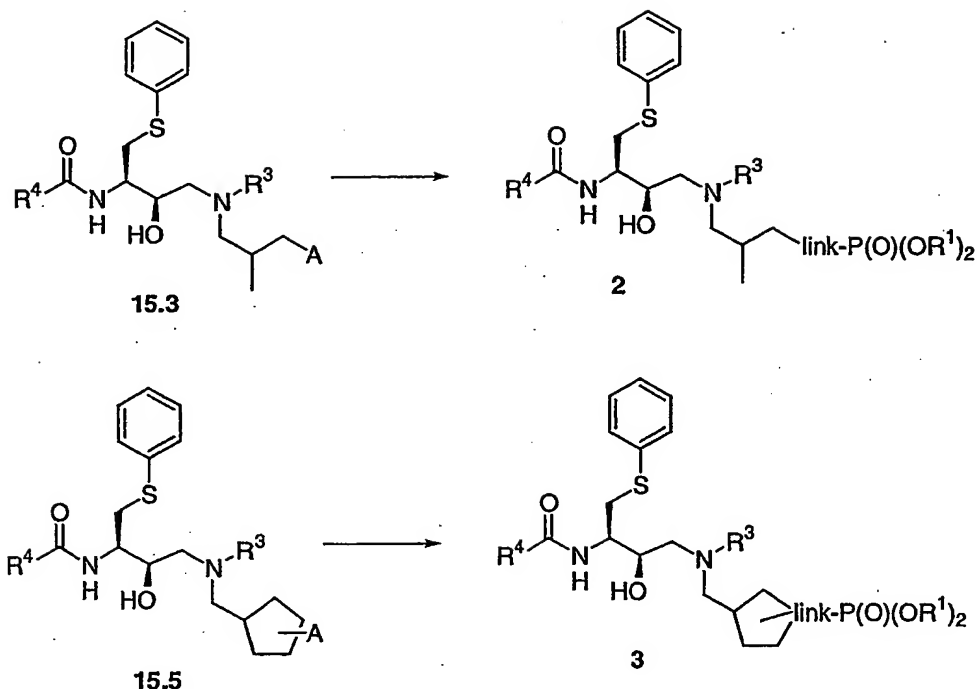
Scheme 15



Scheme 16

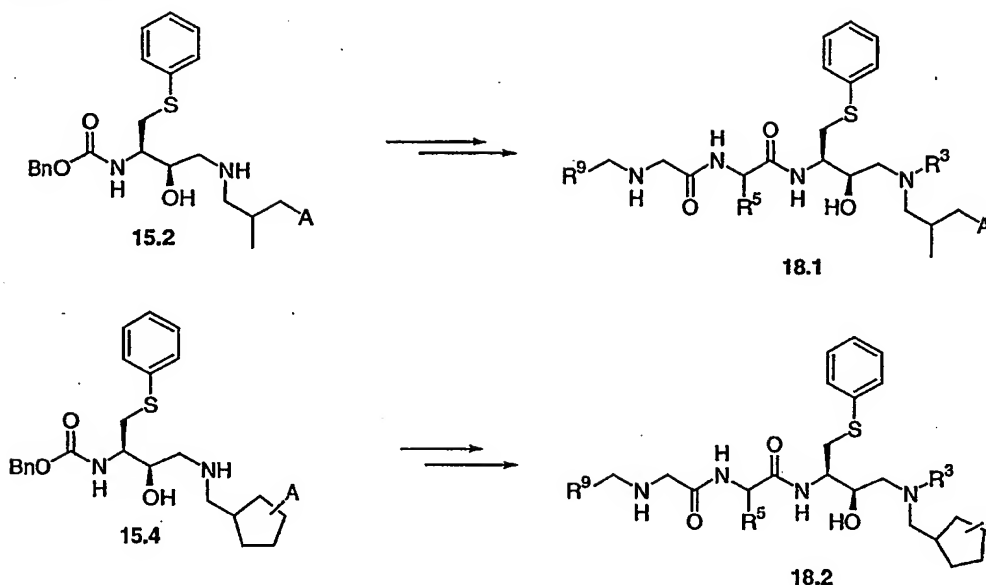


Scheme 17

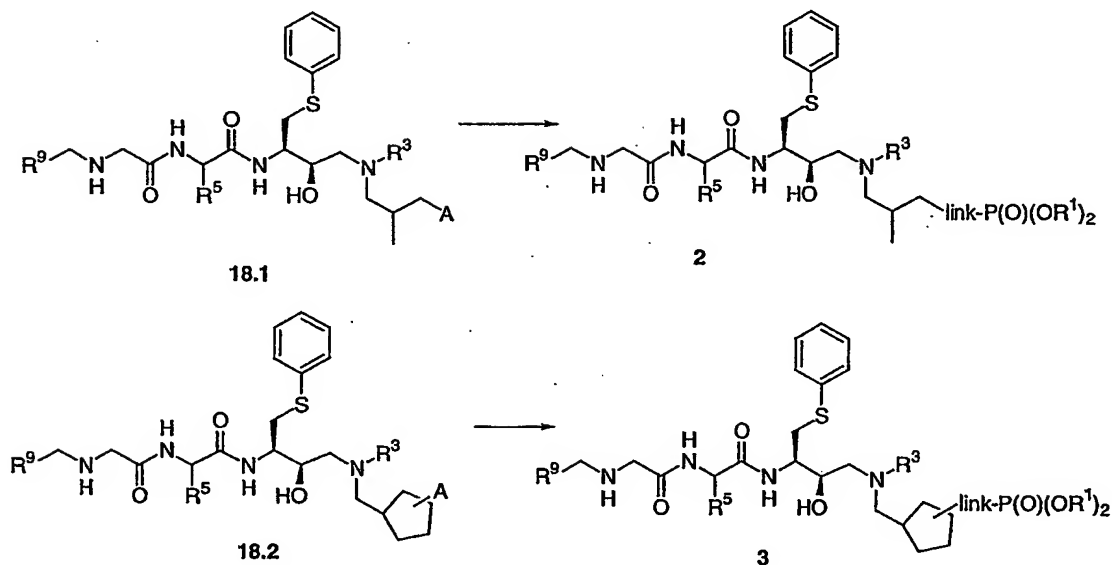


- Scheme 18-19 depict the preparation of phosphonate esters 2 and 3, in which the group A is attached to a sulfur linked aryl moiety, and the $R_4\text{COOH}$ group contains a amine group. The amines 15.2 and 15.4, in which substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, prepared in Scheme 15, are converted using the same conditions described in Scheme 7 for the preparation of the amine 7.10 from 7.8 and Scheme 9a for the preparation of 9a.4 from 7.10 to give 18.1 and 18.2 respectively.
- The reactions shown in Scheme 18 illustrate the preparation of the compound 18.1 and 18.2 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 19 depicts the conversion of 18.1 and 18.2 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 2 and 3 respectively in which X is sulfur. In this procedure 18.1 and 18.2 are converted, using the procedures described below, Schemes 47-99, into the compounds 2 and 3

Scheme 18



Scheme 19



Preparation of the phosphonate ester intermediates 4 in which X is a direct bond

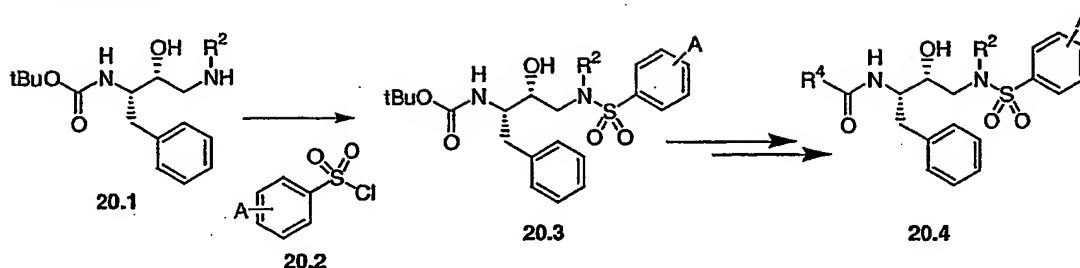
- 5 Schemes 20-22 illustrate the preparation of the phosphonate esters 4 in which X is a direct bond and the R group does not contain a primary or secondary amine group. As shown in Scheme 20, the amine 20.1 is reacted with the sulfonyl chloride 20.2 in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, to

afford the product 20.3. The reaction is performed under the same conditions as described above, Scheme 1 for the preparation of the sulfonamide 1.5. Amine 20.1 is prepared by treatment of epoxide 10.1 with the amine 1.2 as described in Scheme 1 for the preparation of 1.3. The preparation of sulfonyl chloride 20.2 is described in Schemes 92-97. The product
5 20.3 is then transformed, using the sequence of reactions described above, Scheme 1, for the conversion of the amide 1.5 into the amide 1.8, into the product 20.4.

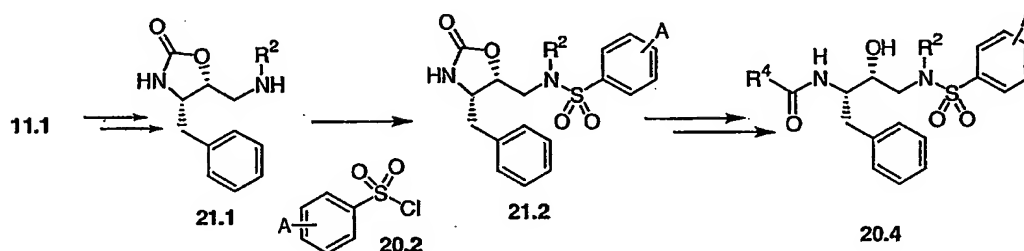
An alternative route to the product 20.4 is shown in Scheme 21 in which amine 11.1 is treated under conditions described in Scheme 2 with the amine 1.2 to give the amine 21.1. The amine
10 21.1 is then sulfonylated with 20.2 in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme 2, to afford the product 21.2. The product 21.2 is then converted as described above, Scheme 2, into the sulfonamide 20.4.

15 The reactions shown in Scheme 20 and 21 illustrate the preparation of the compound 20.4 in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 22 depicts the conversion of this compounds 20.4 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 4 respectively, in which X is a direct bond. In this procedure, the amines 20.4 is converted, using the procedures described below,
20 Schemes 47-99, into the compounds 4.

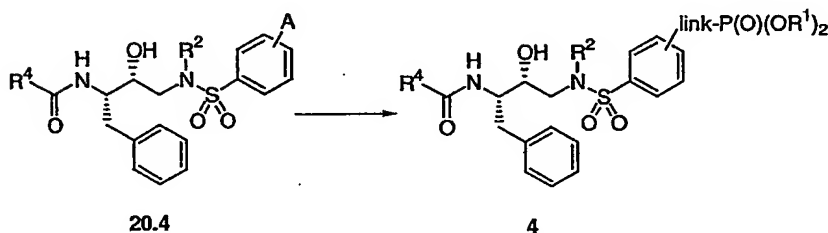
Scheme 20



Scheme 21



Scheme 22

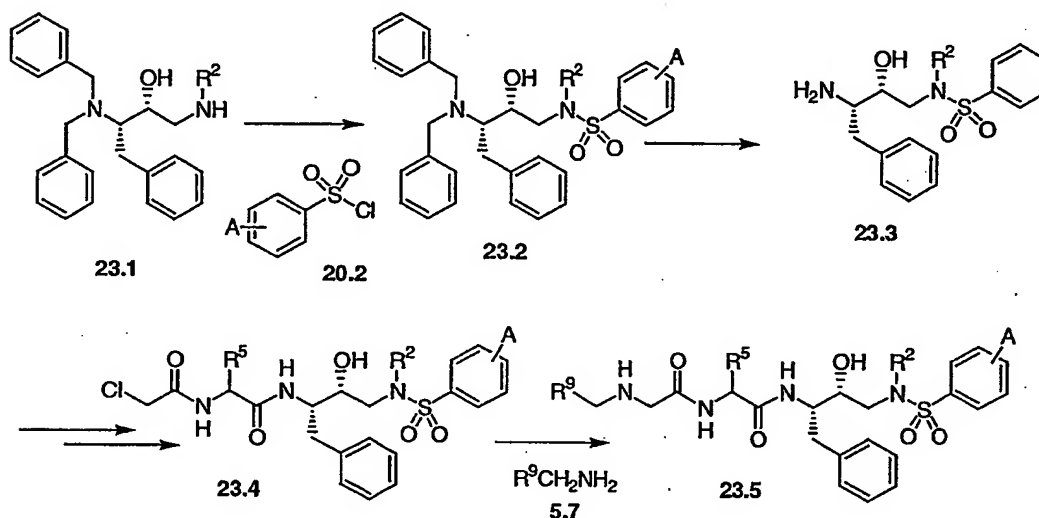


Schemes 23 illustrates the preparation of the phosphonate esters 4 in which X is a direct bond and the R₄COOH group contains an amine group. The amine 23.1, prepared from the epoxide 13.1 and an amine 1.2 as described in Scheme 13 for the synthesis of 13.2 from 13.1, is reacted with the sulfonyl chloride 20.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, as described in Schemes 1 for the synthesis of 1.5, to give the product 23.2. The product 23.2 is then reduced to amine 23.3 according to the conditions described in Scheme 3 for the preparation of 3.4 from 3.3. The amine product is then converted as described in Scheme 5 into the chloride 23.4. The chloride is treated with the amine 5.7 to afford the amine 23.5, as described in Scheme 5 for the preparation of 5.8 from 5.7.

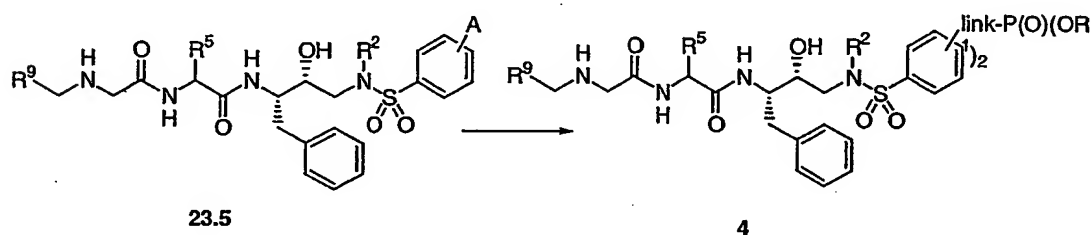
The reactions shown in Scheme 23 illustrate the preparation of the compound 23.5 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as $[\text{OH}]$, $[\text{SH}]$, $[\text{NH}]$, Br etc. Scheme 24 depicts the conversion of the compound 23.5 in which A is $[\text{OH}]$, $[\text{SH}]$, $[\text{NH}]$, Br etc, into the phosphonate esters 4 in which X is a direct bond. In this

5 procedure, the compound 23.5 is converted, using the procedures described below, Schemes 47-99, into the compound 4.

Scheme 23



Scheme 24



10 Preparation of the phosphonate ester intermediates 4 in which X is a sulfur

The intermediate phosphonate ester 4, in which the group A is attached to a sulfur linked aryl moiety, and the R_4COOH group does not contain an amine is prepared as shown in Schemes 25-27. Amine 25.1 prepared from epoxide 15.1 and amine 1.2 as described in Scheme 15 is

5 treated with sulfonamide 20.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, using the conditions described in Scheme 7, to give the sulfonamide 25.2. The sulfonamide 25.2 is then converted as described in Scheme 7 for the conversion of 7.9 to 7.10, and Scheme 9a for the conversion of 7.10 into 9a.4, to the product 25.3. Alternatively, Scheme 26, illustrates how the amine 8.5 prepared according to Scheme 8 is reacted with 20.2 under conditions described in Scheme 8 for the preparation of 8.6 from 8.5, to give the sulfonamide 26.1. Further modification according to the conditions described in Scheme 8 for the preparation of 7.11, affords sulfonamide 25.3.

10 The reactions shown in Scheme 25-26 illustrate the preparation of the compounds sulfonamide 25.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 27 depicts the conversion of 25.3 in which A is [OH], [SH], [NH], Br etc, into the phosphonate 4 in which X is sulfur. In this procedure 25.3 is converted, using the procedures described below, Schemes 47-99, into the compound 4.

15

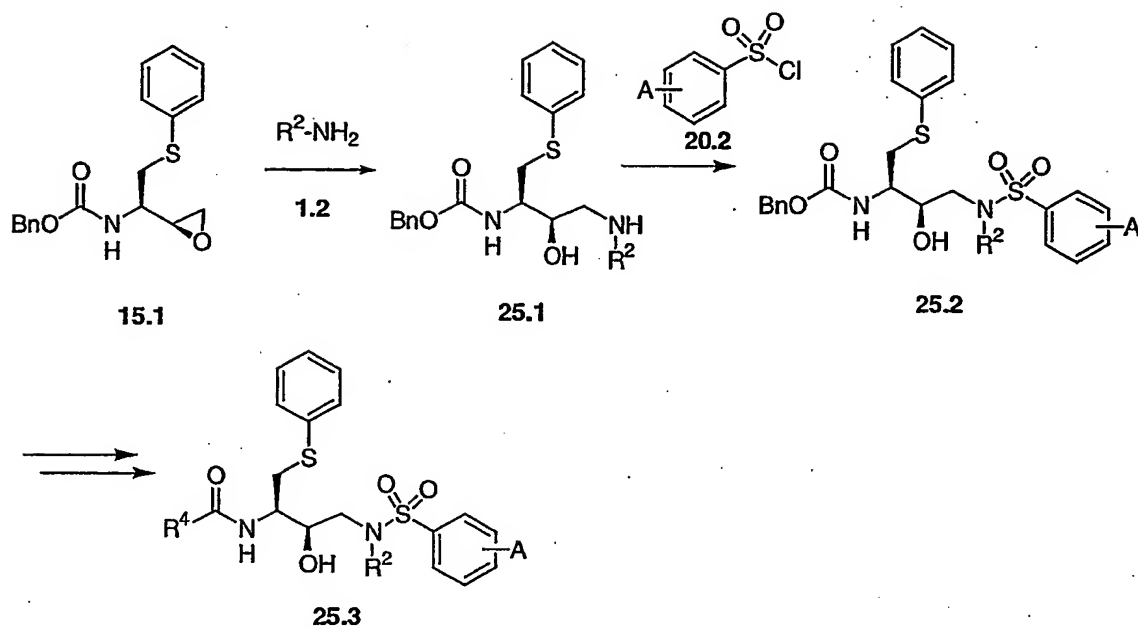
Preparation of the intermediate phosphonate ester 4, in which the group A is attached to a sulfur linked aryl moiety, and the R₄COOH group contains an amine are prepared as shown in Schemes 28-29. Amine 25.2 (Scheme 25) in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, is converted to 28.1 as

20 described in Scheme 7 for the preparation of the amine 7.10 from 7.9 and Scheme 9a for the preparation of 9a.4 from 7.10.

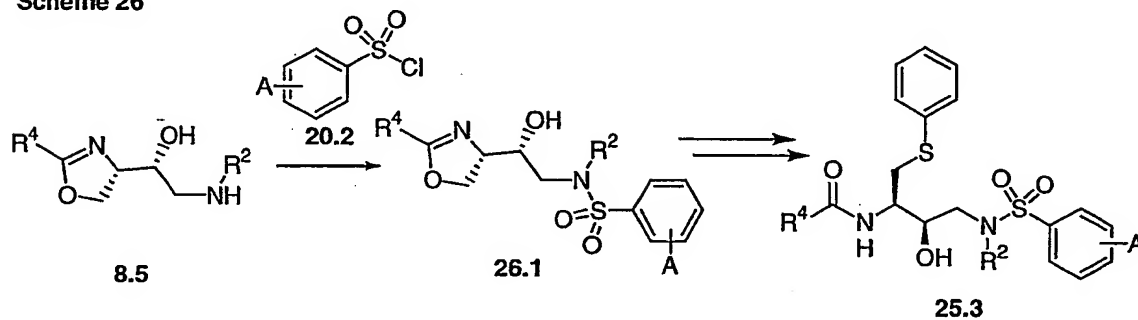
The reactions shown in Scheme 28 illustrate the preparation of the compounds sulfonamide 28.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 29 depicts the conversion of 28.1 in which A is [OH], [SH], [NH], Br etc, into the phosphonate 4 in which X is sulfur. In this procedure 28.1 is converted, using the procedures described below, Schemes 47-99, into the compound 4.

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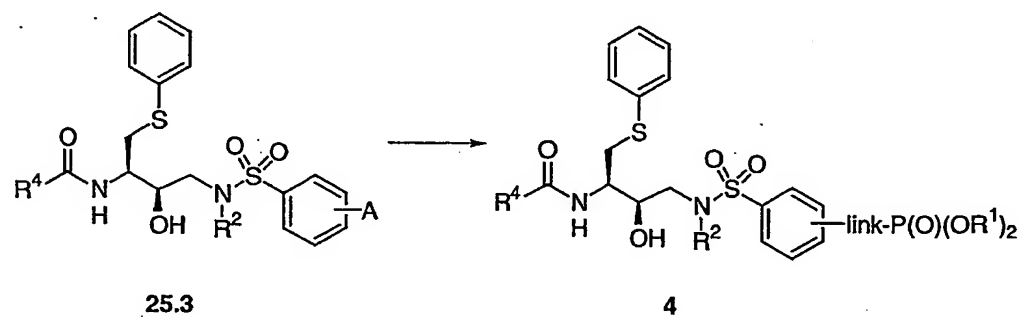
Scheme 25



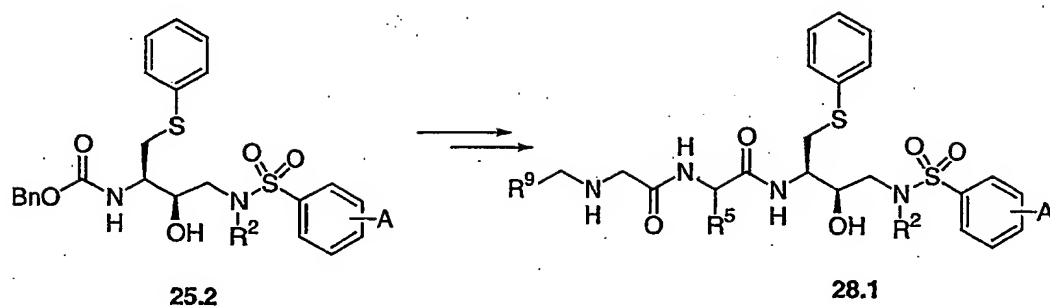
Scheme 26



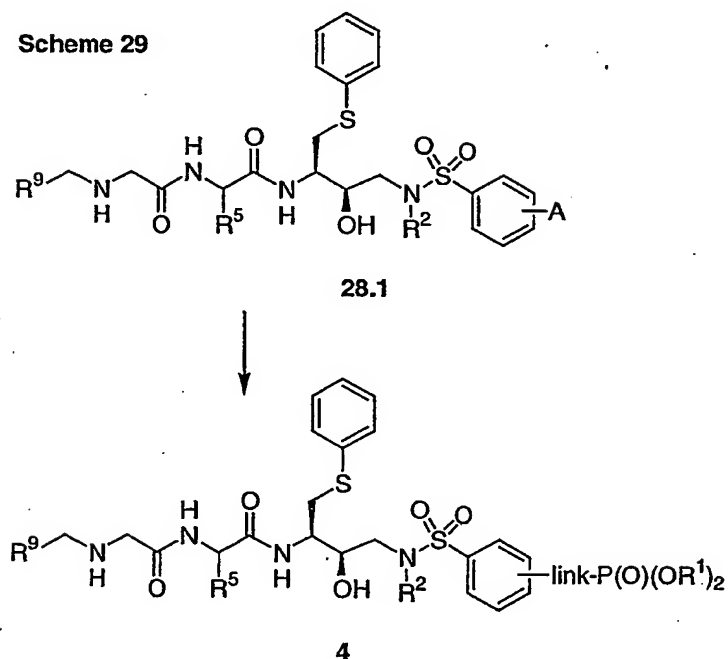
Scheme 27



Scheme 28



Scheme 29



Preparation of the phosphonate ester intermediates 5 in which X is a direct bond

- 5 Schemes 30 illustrates the preparation of the phosphonate esters 5 in which X is a direct bond and the R group does not contain a primary or secondary amine group. As shown in Scheme 30, the amine 23.1 (Scheme 23) is reacted with the alcohol 30.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, to afford the carbamate 30.2. The reaction is performed under conditions described below, Scheme 98,
- 10 for making carbamates from amines and alcohols. The preparation of the 30.1 is described in

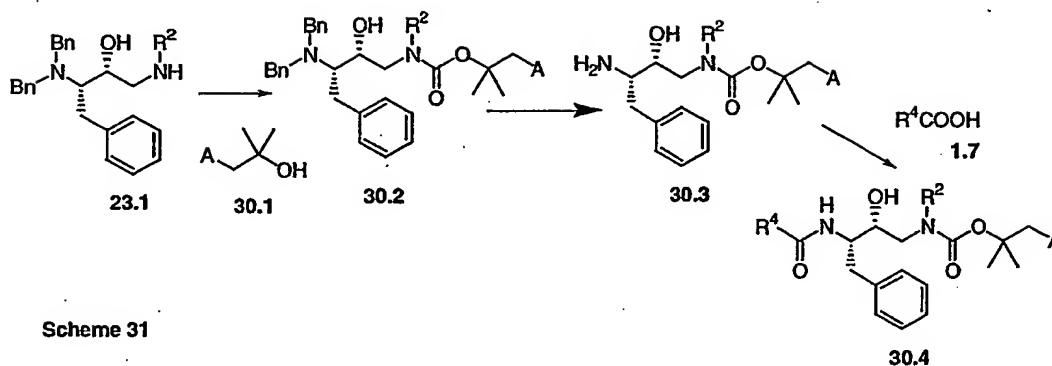
Schemes 83-86. The carbamate 30.2 is then deprotected using conditions described in Scheme 3 for removal of the benzyl groups to give 30.3. Treatment of 30.3 with the R^4COOH acid 1.7 using the conditions described in Scheme 1 then afford the amide 30.4

5 The reactions shown in Scheme 30 illustrate the preparation of the compound 30.4 in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 31 depicts the conversion of this compounds 30.4 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 5 respectively, in which X is a direct bond. In this procedure, the amines 30.4 is converted, using the procedures described below, Schemes
10 47-99, into the compounds 5.

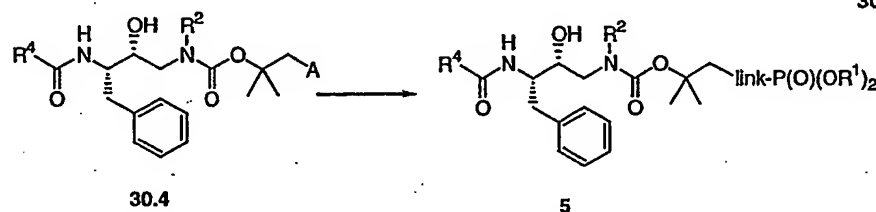
Schemes 32 illustrates the preparation of the phosphonate esters 5 in which X is a direct bond and the R_4COOH group contains an amine. The carbamate 30.2 in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, is
15 converted into the chloride 32.1 using conditions as described in Scheme 9a. Chloride 32.1 is then treated with amine 5.7 to give the amine 32.2, as described in Scheme 9a for the conversion of 7.10 into 9a.3.

The reactions shown in Scheme 32 illustrate the preparation of the compound 32.2 in which
20 the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 33 depicts the conversion of the compound 32.2 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 5 in which X is a direct bond. In this procedure, the compound 32.2 is converted, using the procedures described below, Schemes
25 47-99, into the compound 5.

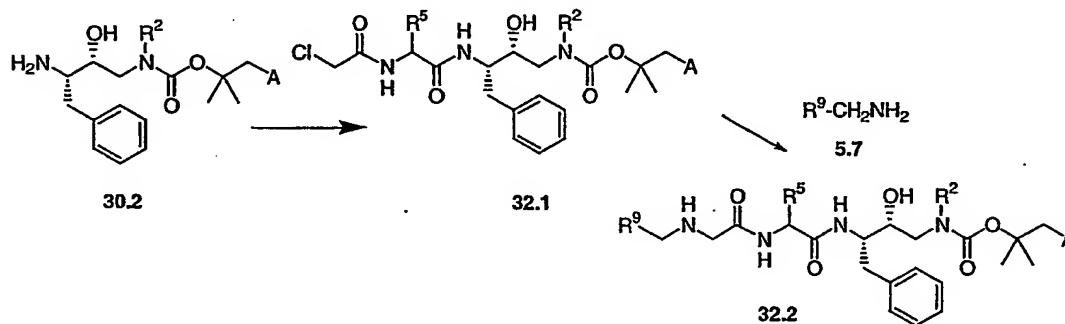
Scheme 30



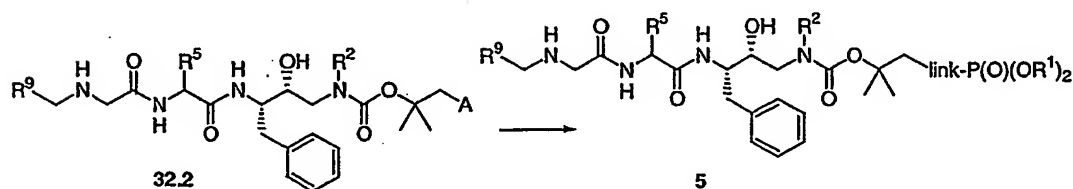
Scheme 31



Scheme 32



Scheme 33



Preparation of the phosphonate ester intermediates 5 in which X is a sulfur

- 5 The intermediate phosphonate ester 5, in which the group A is attached to a sulfur linked aryl moiety, is prepared as shown in Schemes 34-36. Amine 25.1 prepared according to Scheme 25, is treated with alcohol 30.1 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, using the conditions described below ,

Scheme 98, to give the carbamate 34.1. The carbamate 34.1 is then converted as described in Scheme 7, for the conversion of 7.9 to 7.11, to the product 34.2. Alternatively the amine 8.5 prepared according to Scheme 8 can be reacted with alcohol 30.1 under conditions described in Scheme 98 to give the carbamate 35.1. Further modification according to the conditions described in Scheme 8, except incorporating thiophenol, then affords sulfonamide 34.2.

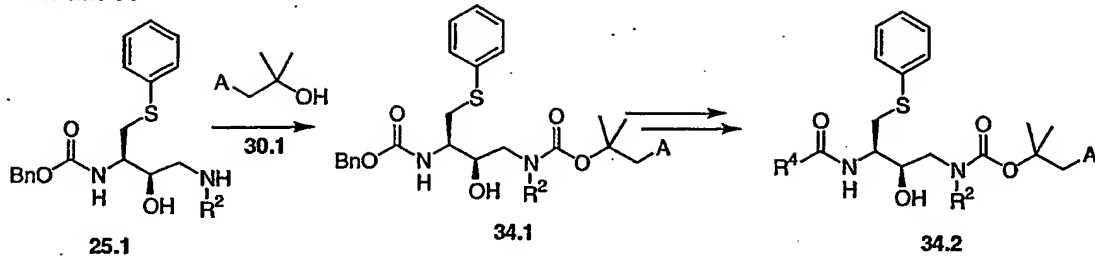
The reactions shown in Scheme 34-35 illustrate the preparation of the compounds sulfonamide 34.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 36 depicts the conversion of 34.2 in which A is [OH], [SH], [NH], Br etc, into the phosphonate 5 in which X is sulfur. In this procedure 34.2 is converted, using the procedures described below, Schemes 47-99, into the compound 5.

Preparation of the intermediate phosphonate ester 5, in which the group A is attached to a sulfur linked aryl moiety, and the R₄COOH group contains an amine are prepared as shown in Schemes 37-38. Carbamate 34.1 (Scheme 35) in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, is converted to 37.1, as described in Scheme 7 for the preparation of the amine 7.10 from 7.9 and Scheme 9a for the preparation of 9a.4 from 7.10..

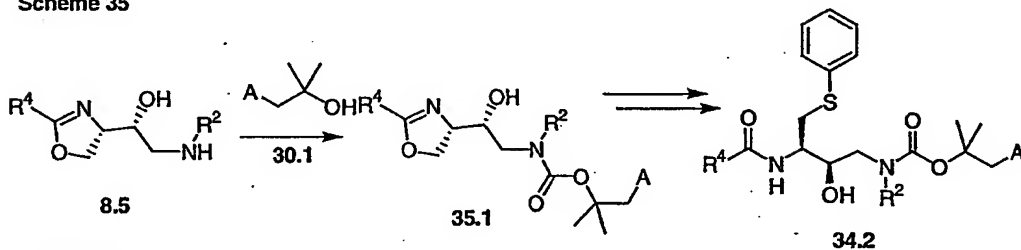
The reactions shown in Scheme 37 illustrate the preparation of the compounds sulfonamide 37.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 38 depicts the conversion of 37.1 in which A is [OH], [SH], [NH], Br etc, into the phosphonate 5 in which X is sulfur. In this procedure 37.1 is converted, using the procedures described below, Schemes 47-99, into the compound 5.

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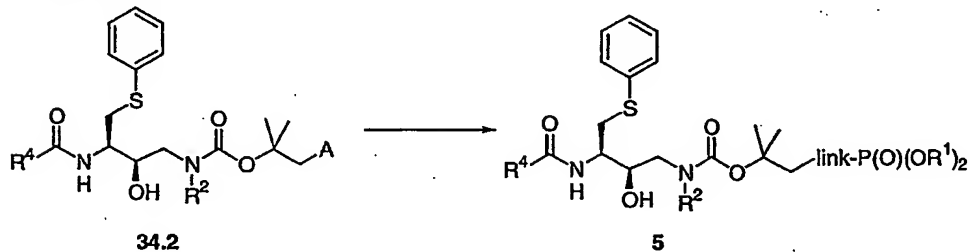
Scheme 34



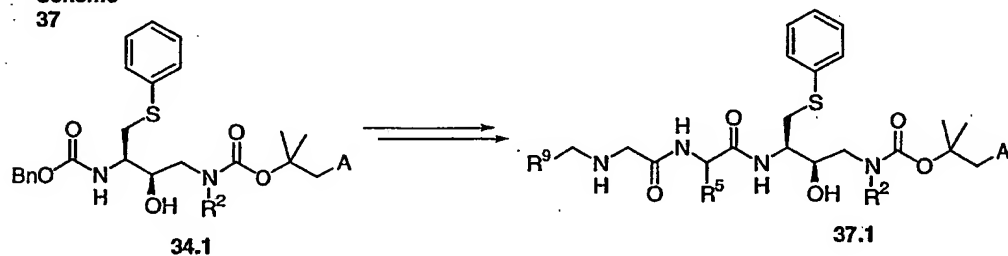
Scheme 35



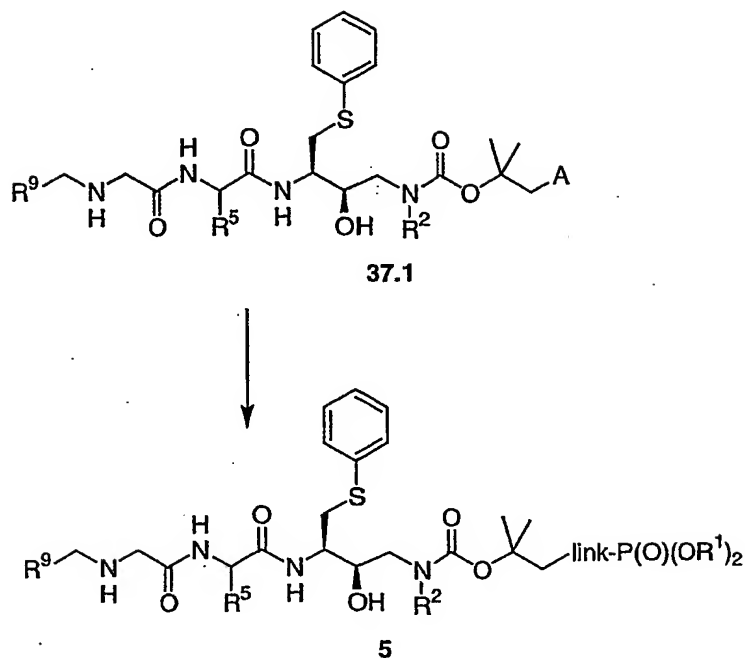
Scheme 36



Scheme 37



Scheme 38

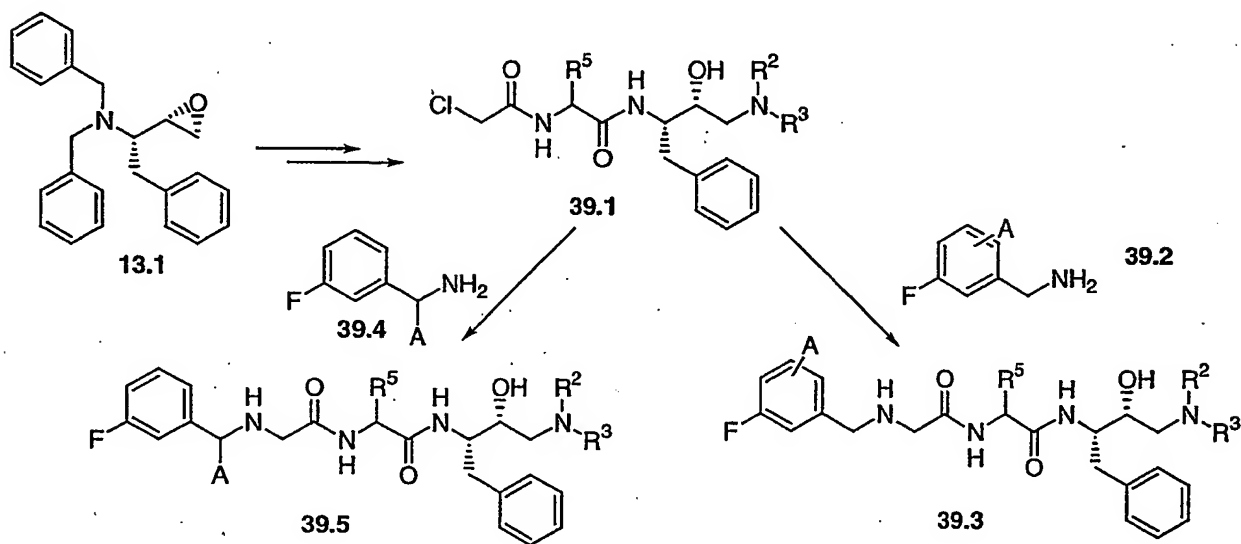


Preparation of the phosphonate ester intermediates 6 and 7 in which X is a direct bond

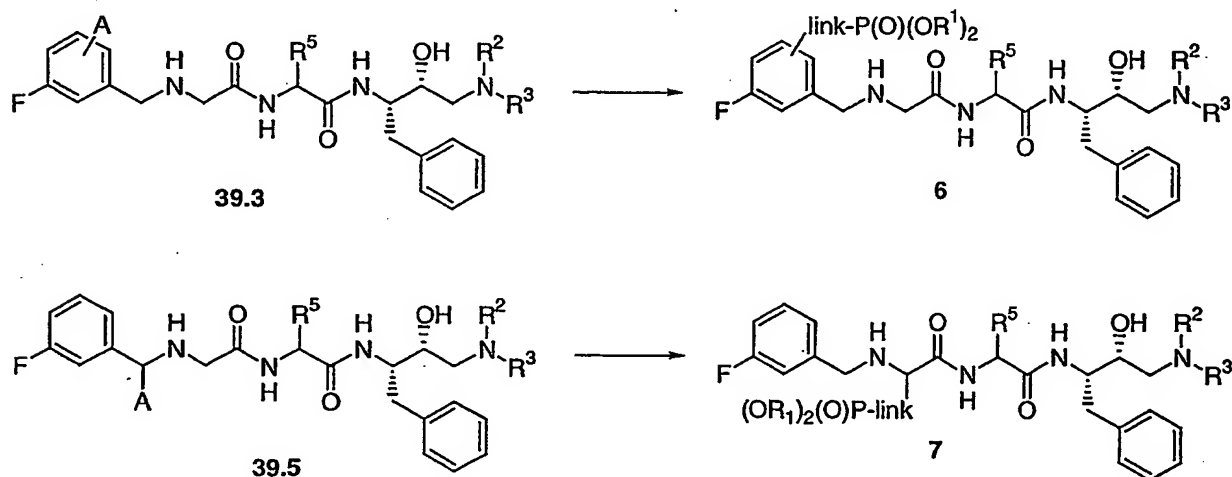
- 5 Schemes 39-40 illustrate the preparation of the phosphonate esters 6 and 7 in which X is a direct bond. As shown in Scheme 39, the epoxide 13.1, prepared as described in Scheme 13 is converted to the chloride 39.1, as described in Scheme 3, for the preparation of 3.4, and Scheme 5, for the conversion of 3.4 into 5.6. The chloride 39.1 is then reacted with the amine 39.2 or 39.4, in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor
- 10 such as [OH], [SH], [NH], Br etc, to afford the amine 39.3 and 39.5 respectively. The reaction is performed under the same conditions as described above, Scheme 5 for the preparation of the amine 5.8 from 5.6. The preparation of 39.2 and 39.4, amines in which A is $\text{link-P(O)(OR}^1)_2$, are shown in Schemes 79-80 and Schemes 81-82 respectively.
- 15 The reactions shown in Scheme 39 illustrate the preparation of the compounds 39.3 and 39.5 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 40 depicts the conversion of these compounds 39.3 and 39.5 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 6 and 7 respectively, in

which X is a direct bond. In this procedure, the amines 39.3 and 39.5 are converted, using the procedures described below, Schemes 47-99, into the compounds 6 and 7 respectively.

Scheme 39



Scheme 40



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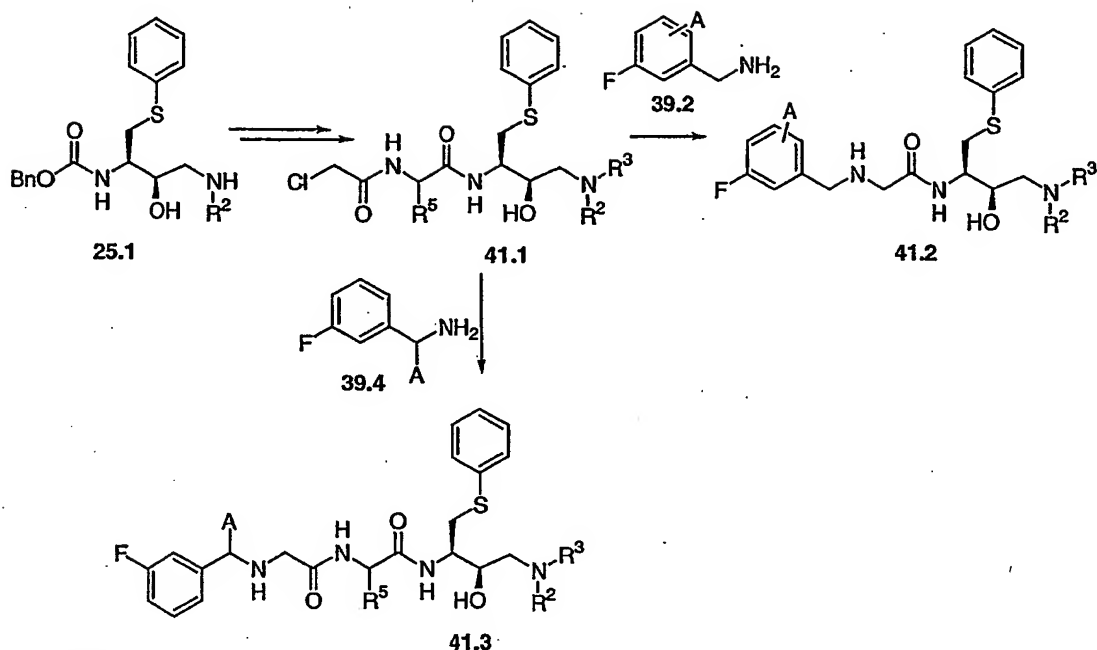
Preparation of the phosphonate ester intermediates 6 and 7 in which X is a sulfur

The intermediate phosphonate esters 6 and 7, in which the group A is attached to a sulfur linked aryl moiety, are prepared as shown in Scheme 41-42. The amine 25.1 (Scheme 25) is

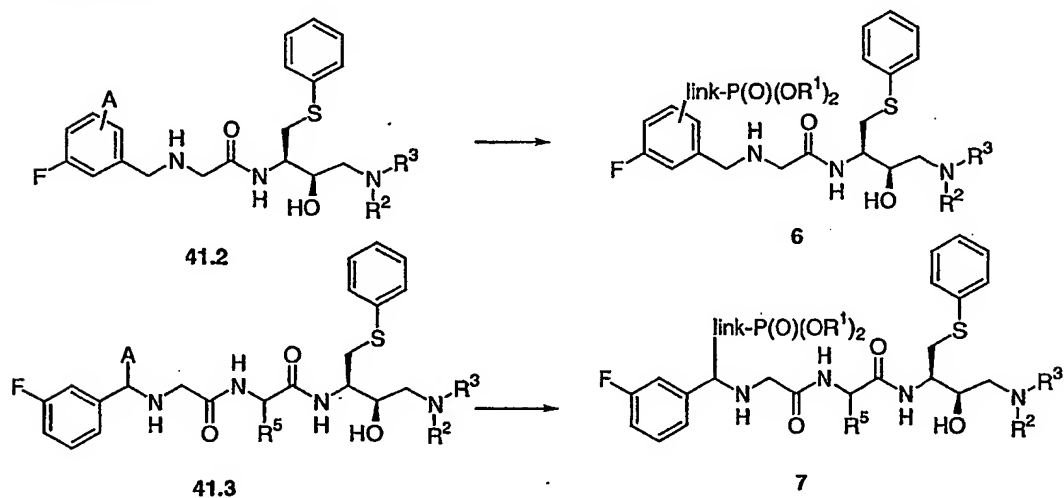
converted to the chloride **41.1** as described in Scheme 7 for the preparation of **7.10** from **7.8**, and Scheme 9a for conversion of **7.10** to **9a3**. The chloride **41.1** is then treated with amine **39.2** or amine **39.4**, in which substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme 5, to give the amines **41.2** and **41.3** respectively.

The reactions shown in Scheme 41 illustrate the preparation of the compounds **41.2** and **41.3** in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 42 depicts the conversion of **41.2** and **41.3** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **6** and **7** in which X is sulfur. In this procedure **41.2** or **41.3** is converted, using the procedures described below, Schemes 47-99, into the compound **6** and **7**.

Scheme 41



Scheme 42



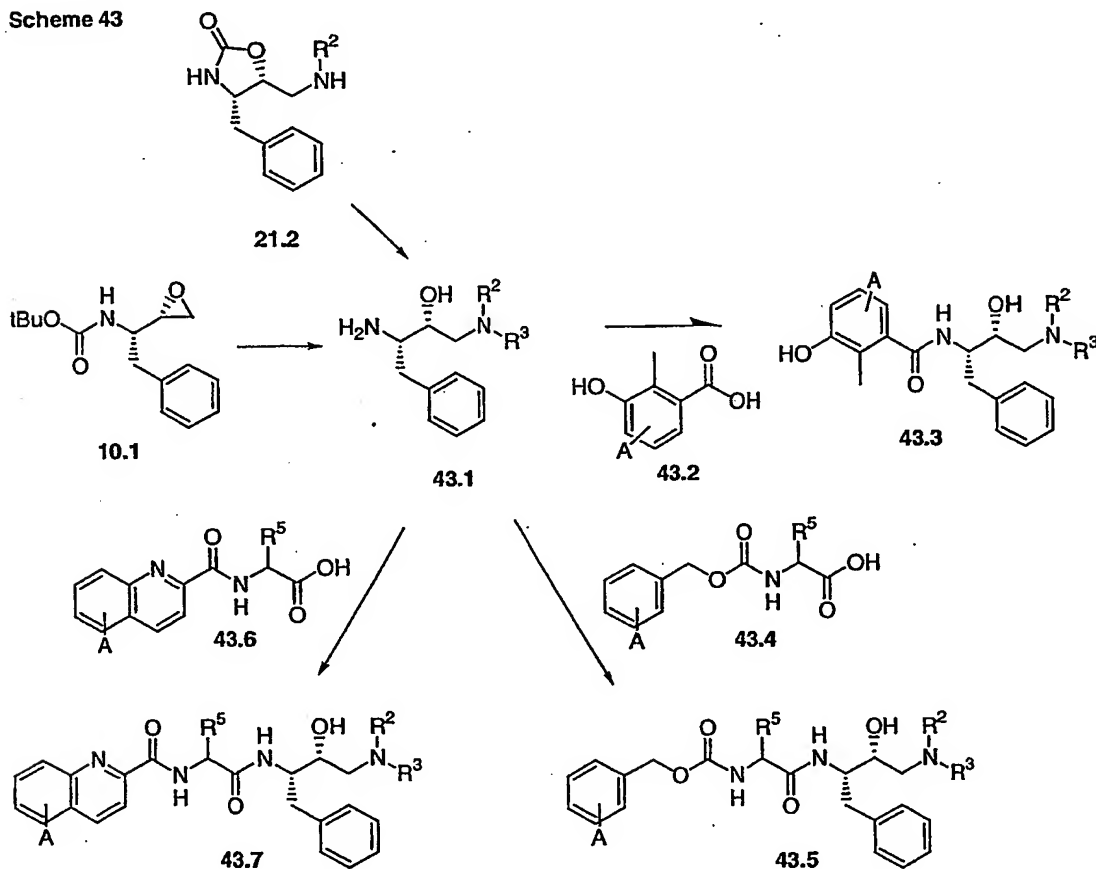
Preparation of the phosphonate ester intermediates 8-10 in which X is a direct bond

- 5 Schemes 43-44 illustrate the preparation of the phosphonate esters 8-10 in which X is a direct bond. As shown in Scheme 43, the amine 43.1 prepared from 10.1 or 21.2 is reacted with the acid 43.2, 43.4 or 43.6, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, to afford the amide 43.3, 43.5 and 43.7 respectively. The reaction is performed under the same conditions as described above, Scheme

1 for the preparation of the amide 1.8. Amine 43.1 is prepared from epoxide 10.1 using the conditions described in Scheme 1 except utilising 10.1 in place of 1.1. Amine 43.1 is prepared from 21.2 according to the conditions described in Scheme 2 except utilizing 21.2 in place of 2.1. The preparation of the acid 43.2 is described in Schemes 47-51, acid 43.4 is described in
 5 Schemes 87-91, and acid 43.6 is described in Schemes 52-55.

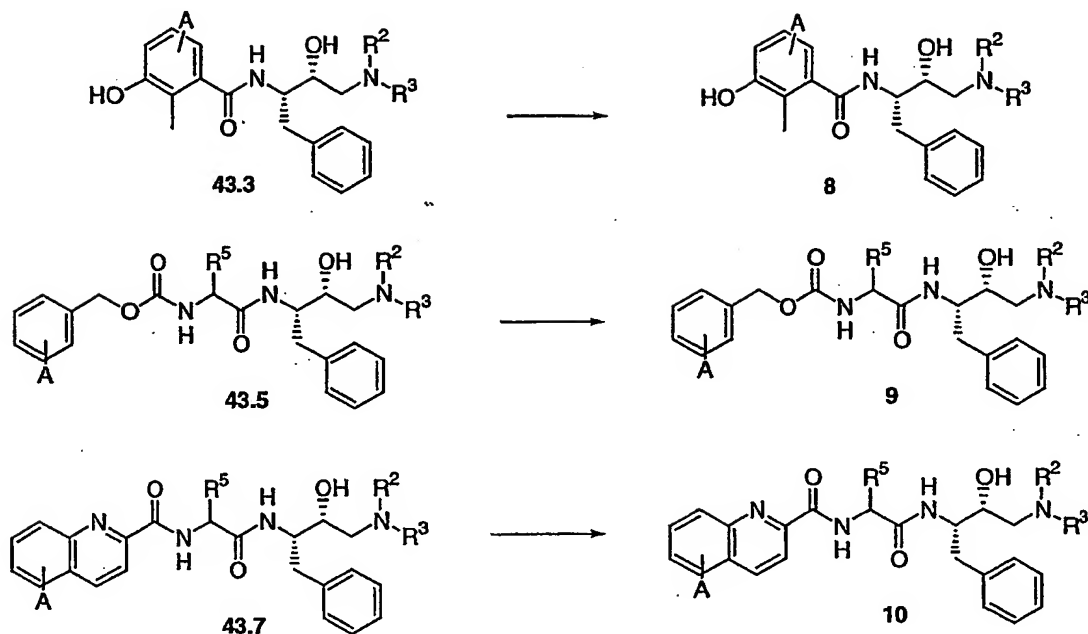
The reactions shown in Scheme 43 illustrate the preparation of the compounds 43.3, 43.5 and 43.7 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 44 depicts the conversion of these compounds 43.3, 43.5,
 10 and 43.7 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 8, 9 and 10 respectively, in which X is a direct bond. In this procedure, the amines 43.3, 43.5 and 43.7 are converted, using the procedures described below, Schemes 47-99, into the compounds 8, 9, and 10 respectively.

Scheme 43



15

Scheme 44



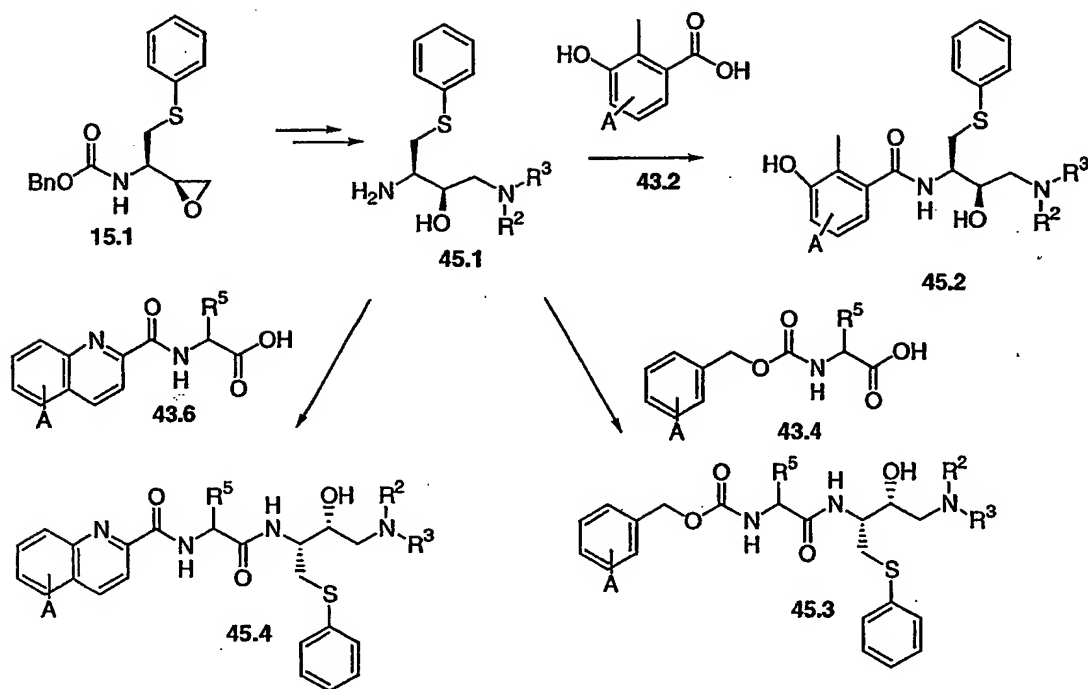
Preparation of the phosphonate ester intermediates 8-10 in which X is a sulfur

- 5 The intermediate phosphonate esters 8-10, in which the group A is attached to a sulfur linked aryl moiety, are prepared as shown in Schemes 45-46. In Scheme 45, epoxide 15.1 is prepared from mesylate 7.1 using the conditions described in Scheme 7 except incorporating thiophenol for thiol 7.2. The epoxide 15.1 is then converted to amine 45.1 according to the conditions described in Scheme 7 for the preparation of 7.10 from 7.7. Amine 45.1 is then
- 10 treated with acids 43.2, 43.4 or 43.6, in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme 7, to give the amides 45.2, 45.3, and 45.4 respectively.

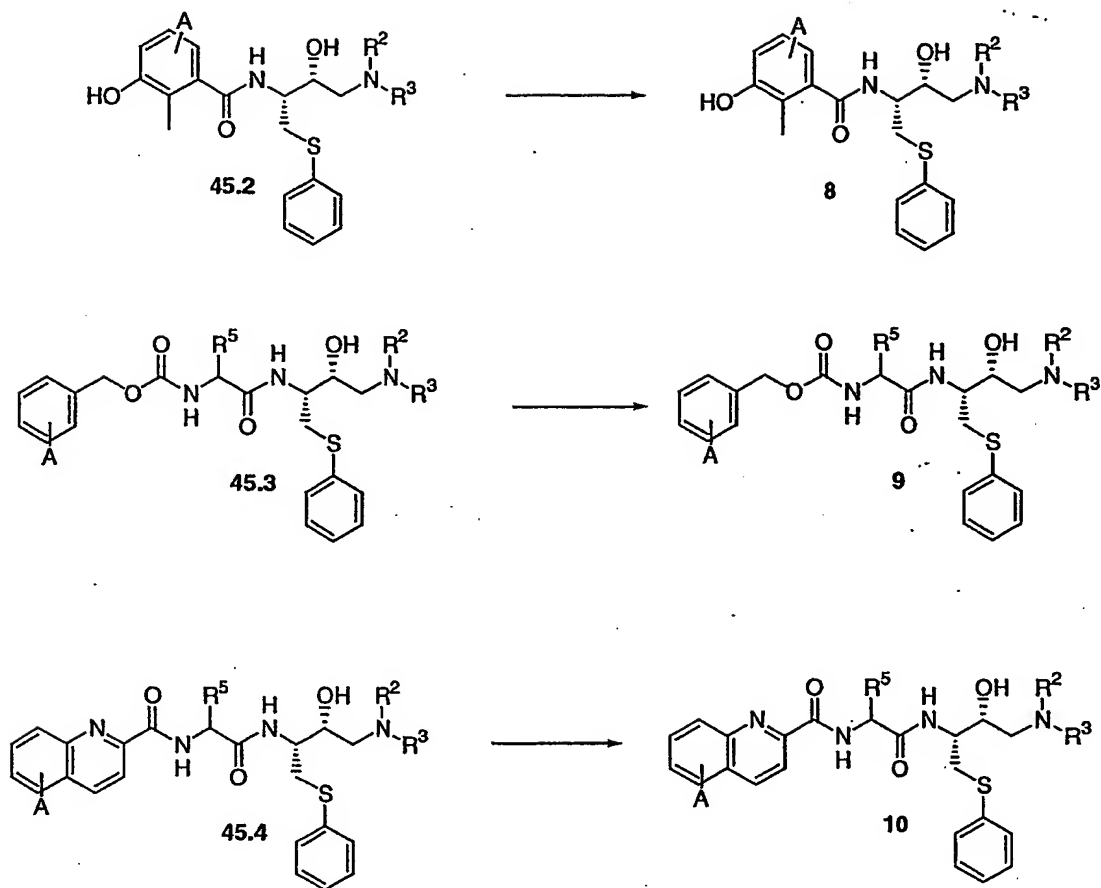
The reactions shown in Scheme 45 illustrate the preparation of the compounds 45.2, 45.3, and

15 45.4 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 46 depicts the conversion 45.2, 45.3, and 45.4 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 8, 9 and 10 respectively in which X is sulfur. In this procedure 45.2, 45.3, and 45.4 is converted, using the procedures described below, Schemes 47-99, into the compounds 8, 9 and 10 respectively.

Scheme 45



Scheme 46



Preparation of phosphonate-containing hydroxymethyl benzoic acids 43.2.

- 5 Schemes 47 - 51 illustrate methods for the preparation of phosphonate-containing hydroxymethyl benzoic acids 43.2 which are employed in the preparation of the phosphonate esters 8.

Scheme 47 illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid 47.1 is subjected to halogen-methyl exchange to afford the organometallic intermediate 47.2. This compound is reacted with a chlorodialkyl phosphite 47.3 to yield the phenylphosphonate ester 47.4, which upon deprotection affords the carboxylic acid 47.5.

10

For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, **47.6**, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Am. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **47.7**, as described in

- 5 Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester **47.8**. This compound is treated with boron trifluoride at 0° to effect rearrangement to the orthoester **47.9**, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether **47.10**. Halogen-metal exchange is performed by the
- 10 reaction of the substrate **47.10** with butyllithium, and the lithiated intermediate is then coupled with a chlorodialkyl phosphite **47.3**, to produce the phosphonate **47.11**. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid **47.12**.
- 15 Using the above procedures, but employing, in place of the bromo compound **47.6**, different bromo compounds **47.1**, there are obtained the corresponding products **47.5**.

Scheme 48 illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

- 20 In this method, a suitably protected dimethyl hydroxybenzoic acid, **48.1**, is reacted with a brominating agent, so as to effect benzylic bromination. The product **48.2** is reacted with a sodium dialkyl phosphite, **48.3**, as described in J. Med. Chem., 1992, 35, 1371, to effect displacement of the benzylic bromide to afford the phosphonate **48.4**. Deprotection of the carboxyl function then yields the carboxylic acid **48.5**.
- 25 For example, 2,5-dimethyl-3-hydroxybenzoic acid, **48.6**, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p.17, to afford the ether ester **48.7**. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or
- 30 diisopropylethylamine. The product **48.7** is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product **48.8**. This compound is then reacted with a sodium dialkyl

phosphite 48.3 in tetrahydrofuran, as described above, to afford the phosphonate 48.9.

Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid 48.10.

Using the above procedures, but employing, in place of the methyl compound 48.6, different
5 methyl compounds 48.1, there are obtained the corresponding products 48.5.

Scheme 49 illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom.

In this method, a suitably protected hydroxy- or mercapto-substituted hydroxy methyl benzoic
10 acid 49.1 is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl hydroxymethyl phosphonate 49.2, to afford the coupled product 49.3, which upon deprotection affords the carboxylic acid 49.4.

For example, 3,6-dihydroxy-2-methylbenzoic acid, 49.5, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester 49.6, by
15 treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 77, to afford the mono-silyl ether 49.7. This compound is then reacted
20 with a dialkyl hydroxymethylphosphonate 49.2, under the conditions of the Mitsunobu reaction. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in
25 an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The reaction affords the coupled product 49.8. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic
30 carboxylic acid 49.9.

Using the above procedures, but employing, in place of the phenol 49.5, different phenols or thiophenols 49.1, there are obtained the corresponding products 49.4.

Scheme 50 depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains.

In this method, a dialkyl alkenylphosphonate 50.2 is coupled, by means of a palladium catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid 50.1. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. The product 50.3 is deprotected to afford the phosphonate 50.4; the latter compound is subjected to catalytic hydrogenation to afford the saturated carboxylic acid 50.5.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid 50.6, prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester 50.7 as described above. This compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate 50.8, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above to afford the product 50.9. Deprotection, or hydrogenation/deprotection, of this compound, as described above, then affords respectively the unsaturated and saturated products 50.10 and 50.11.

Using the above procedures, but employing, in place of the bromo compound 50.6, different bromo compounds 50.1, and/or different phosphonates 50.2, there are obtained the corresponding products 50.4 and 50.5.

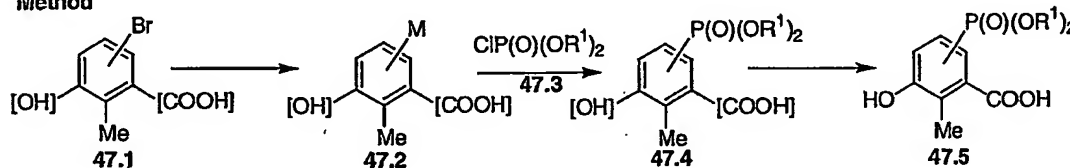
Scheme 51 illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid 51.1 is converted to the corresponding boronic acid 51.2, by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82. The product is subjected to a Suzuki coupling reaction with a dialkyl bromophenyl phosphonate 51.3. The product 51.4 is then deprotected to afford the diaryl phosphonate product 51.5.

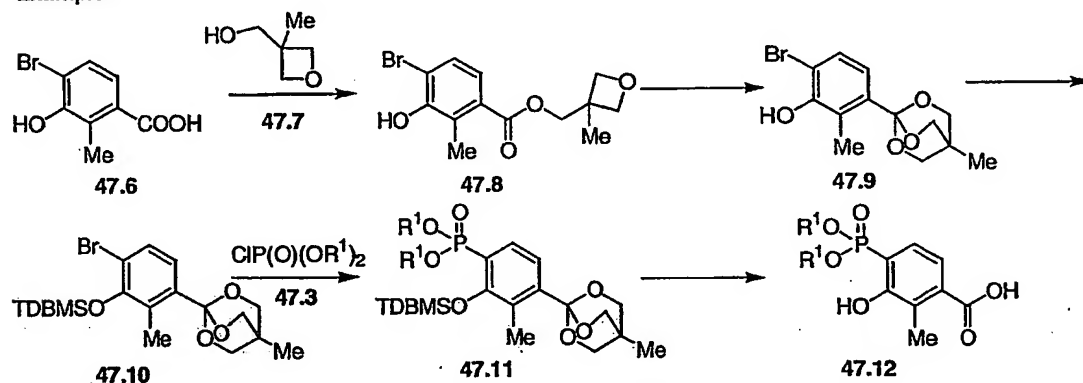
- For example, the silylated OBO ester **51.6**, prepared as described above, (Scheme 47), from 5-bromo-3-hydroxybenzoic acid, the preparation of which is described in J. Labelled. Comp. Radiopharm., 1992, 31, 175, is converted into the boronic acid **51.7**, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate **51.8**, prepared as described in
- 5 J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, in the presence of sodium bicarbonate, as described, for example, in Palladium reagents and catalysts J. Tsuji, Wiley 1995, p 218, to afford the diaryl phosphonate **51.9**. Deprotection, as described above, then affords the benzoic acid **51.10**.
- Using the above procedures, but employing, in place of the bromo compound **51.6**, different
- 10 bromo compounds **51.1**, and/or different phosphonates **51.3**, there are obtained the corresponding carboxylic acid products **51.5**.

Scheme 47

Method

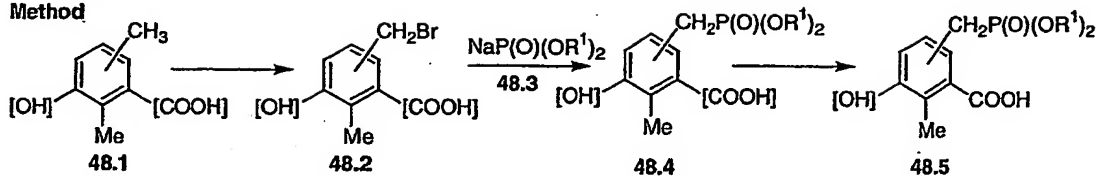


Example

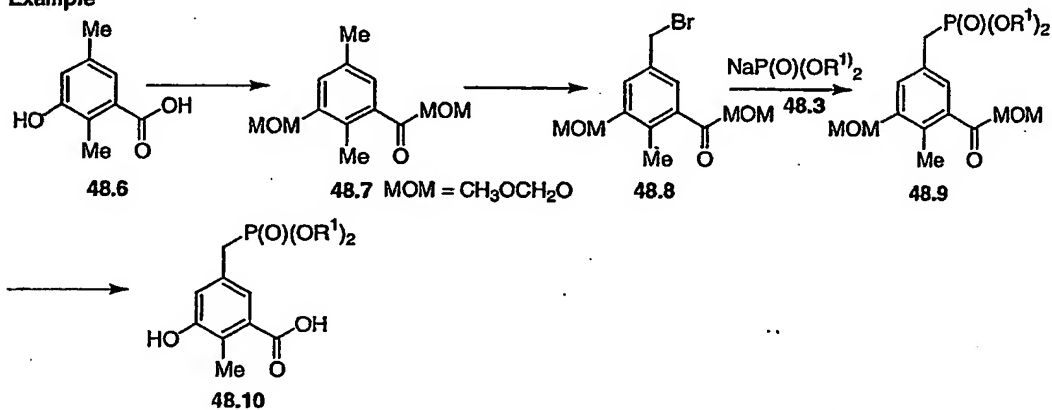


Scheme 48

Method

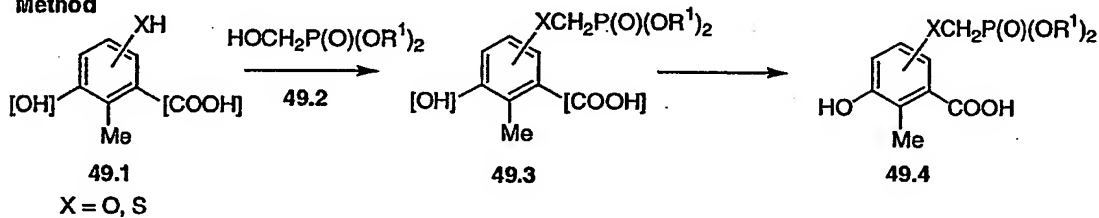


Example

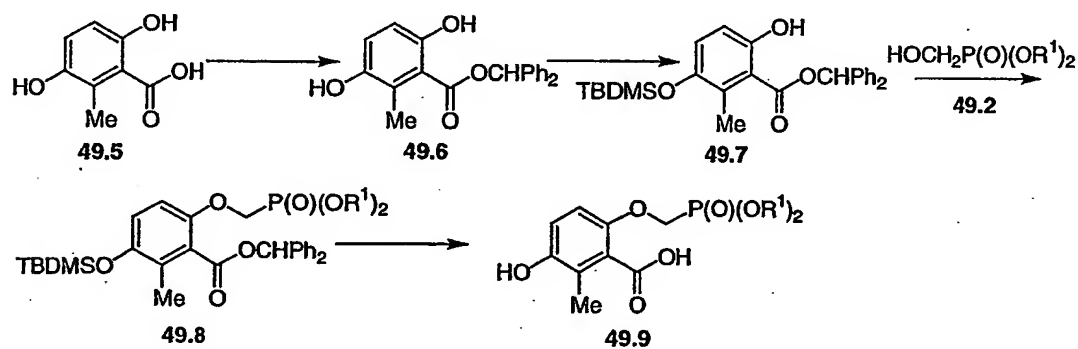


Scheme 49

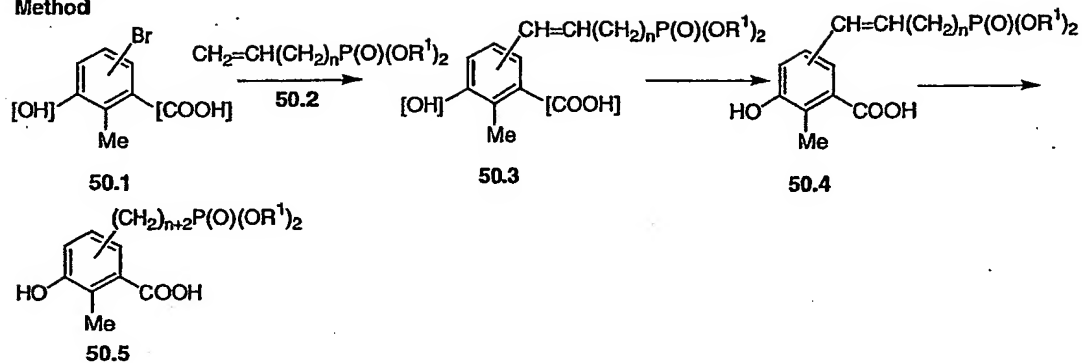
Method



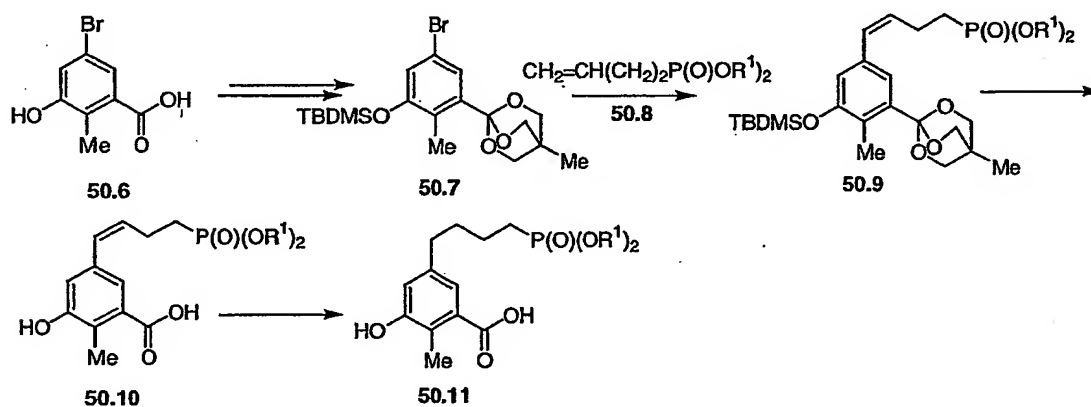
Example



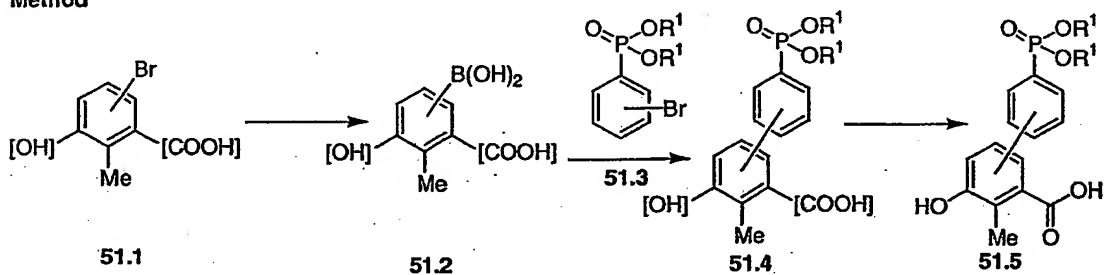
Scheme 50
Method



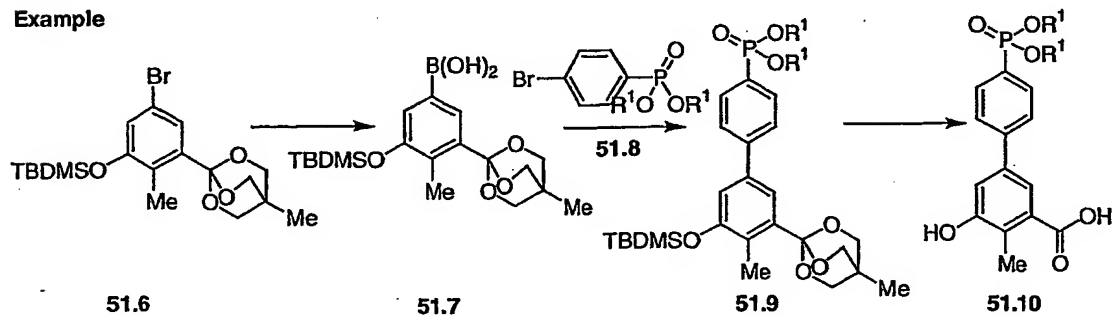
Example



Scheme 51
Method



Example



Preparation of quinoline 2-carboxylic acids 43.6 incorporating phosphonate moieties.

The reaction sequences depicted in Schemes 43 - 46 for the preparation of the phosphonate esters 10 employ a quinoline-2-carboxylic acid reactant 43.6 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br etc. A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het. Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described, for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

Scheme 52 illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde 52.1 is reacted with an alkyl pyruvate ester 52.2, in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester 52.3. Hydrolysis of the ester, for example by the use of aqueous base, then afford the corresponding carboxylic acid 52.4. The carboxylic acid product 52.4 in which X is NH₂ can be further transformed into the corresponding compounds 52.6 in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoroborate, is then heated in aqueous solution, for example as described in Organic

Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol 52.6, Y = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, 52.6, Y = Br. Alternatively, the diazonium tetrafluoroborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to afford the thiol 52.6, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters 52.3 instead of the carboxylic acids 52.5.

For example, 2,4-diaminobenzaldehyde 52.7 (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate 52.2 in methanol, in the presence of a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate 52.8. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid 52.9. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoroborate 52.10 by reaction with sodium nitrite and tetrafluoroboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, 52.11, Z = OH. Alternatively, the diazonium tetrafluoroborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-bromoquinoline-2-carboxylic acid 52.11, Z = Br. Alternatively, the diazonium tetrafluoroborate 52.10 is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid 52.11, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde 52.7, different aminobenzaldehydes 52.1, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids 52.6 are obtained. The variously substituted quinoline carboxylic acids and esters can then be transformed, as described herein, (Schemes 53 – 55) into phosphonate-containing derivatives.

Scheme 53 depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester 53.1 is transformed, via a diazotization procedure as described above (Scheme 52) into the corresponding phenol or

thiol 53.2. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate 53.3, under the conditions of the Mitsunobu reaction, to afford the phosphonate ester 53.4. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 448, and in *Advanced Organic Chemistry, Part B*, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products 53.4. Basic hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid 53.5. The product is then coupled with a suitably protected aminoacid derivative 53.6 to afford the amide 53.7. The reaction is performed under similar conditions to those described above, Scheme 1. The ester protecting group is then removed to yield the carboxylic acid 53.8. For example, methyl 6-amino-2-quinoline carboxylate 53.9, prepared as described in *J. Het. Chem.*, 1989, 26, 929, is converted, by means of the diazotization procedure described above, into methyl 6-mercaptoquinoline-2-carboxylate 53.10. This material is reacted with a dialkyl hydroxymethylphosphonate 53.11 (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether 53.12. Basic hydrolysis then afford the carboxylic acid 53.13. The latter compound is then converted, as described above, into the aminoacid derivative 53.16. Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline carboxylate 53.9, different aminoquinoline carboxylic esters 53.1, and/or different dialkyl hydroxymethylphosphonates 53.3 the corresponding phosphonate ester products 53.8 are obtained.

Scheme 54 illustrates the preparation of quinoline-2-carboxylic acids incorporating phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester 54.1 is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate 54.2. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as

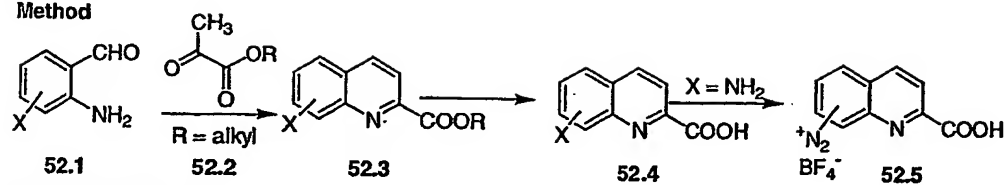
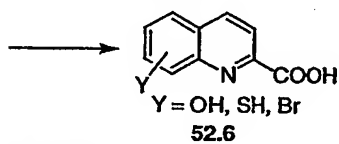
dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Thus, Heck coupling of the bromo compound 54.1 and the olefin 54.2 affords the olefinic ester 54.3. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid 54.4. The latter compound is then transformed, as described above, into the homolog 54.5. Optionally, the unsaturated carboxylic acid 54.4 can be reduced to afford the saturated analog 54.6. The reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5, or catalytically. The product 54.6 is then converted, as described above (Scheme 53) into the aminoacid derivative 54.7.

For example, methyl 7-bromoquinoline-2-carboxylate, 54.8, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60° with a dialkyl vinylphosphonate 54.9 (Aldrich) in the presence of 2 mol% of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product 54.10. The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid 54.11. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product 54.12. The latter compound is then converted, as described above, into the aminoacid derivative 54.13. The unsaturated product 54.11 is similarly converted into the analog 54.14.

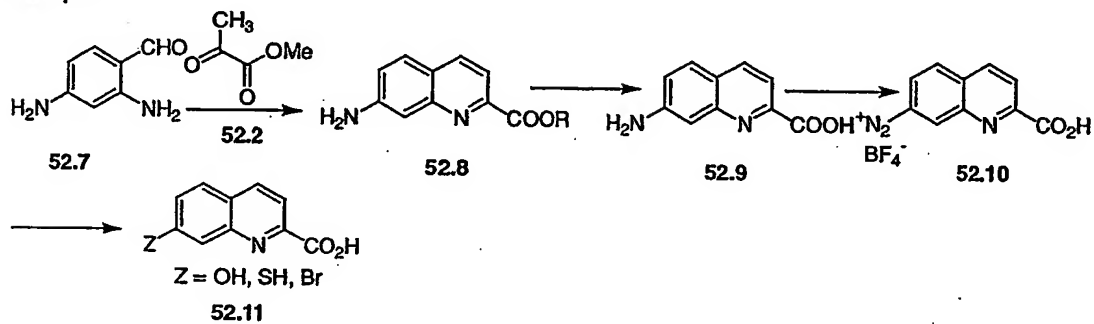
Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate 54.8, different bromoquinoline carboxylic esters 54.1, and/or different dialkyl alkenylphosphonates 54.2, the corresponding phosphonate ester products 54.5 and 54.7 are obtained.

Scheme 52

Method

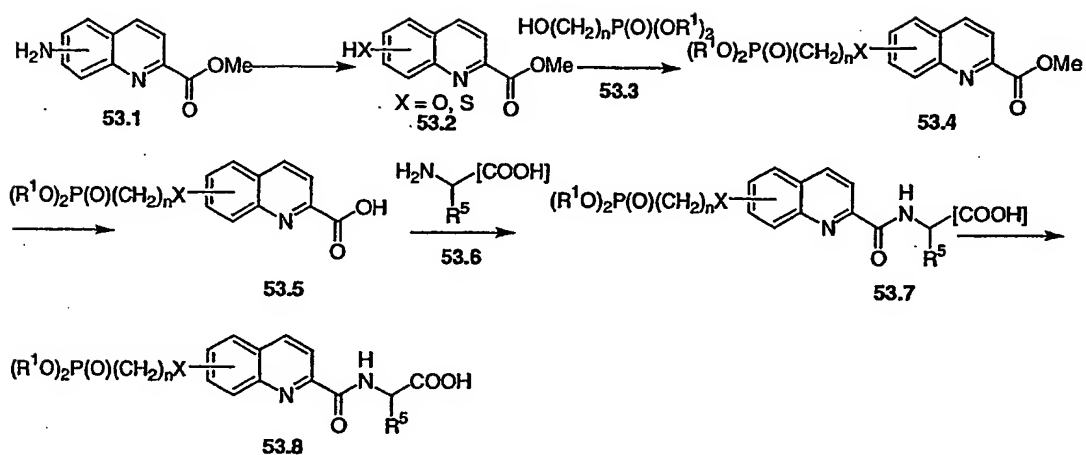
X = OH, SH, NH₂, Br

Example

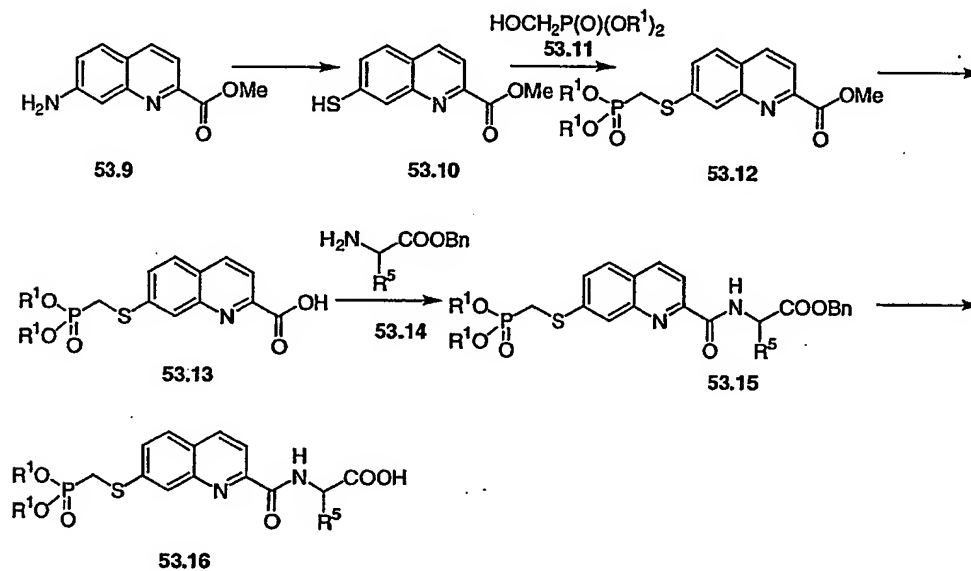


Scheme 53

Method

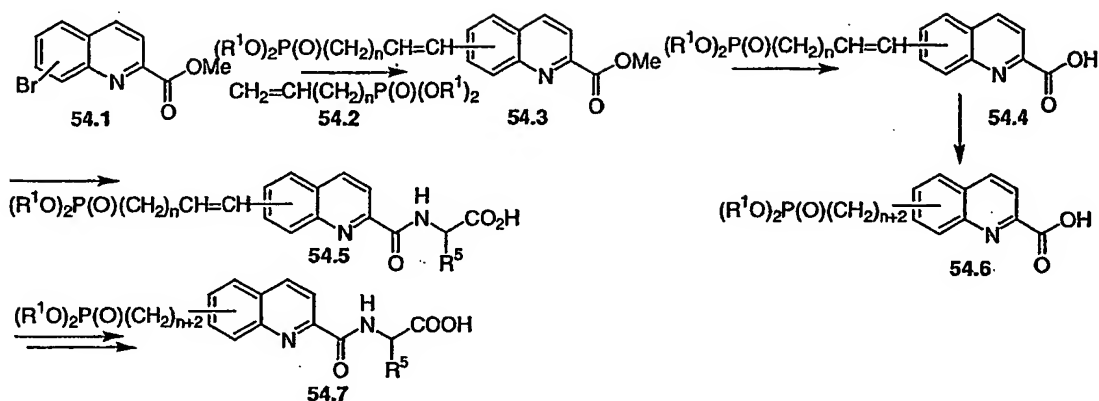


Example

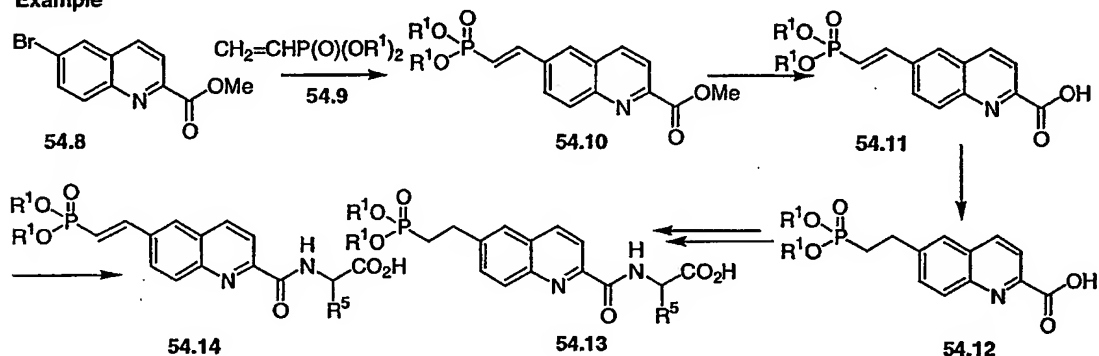


Scheme 54

Method



Example

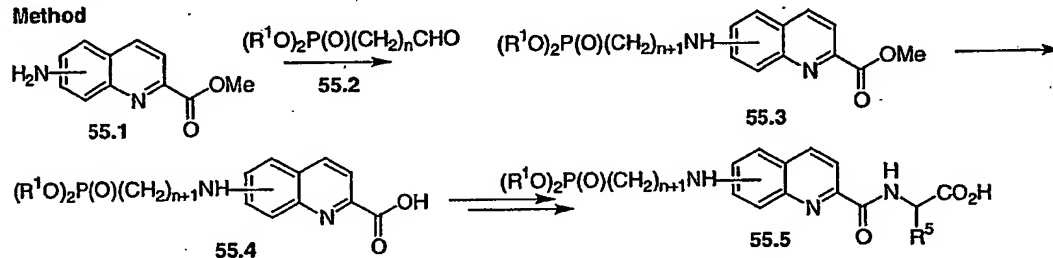


Scheme 55 depicts the preparation of quinoline-2-carboxylic acid derivatives 55.5 in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate 55.1 is reacted with a phosphonate aldehyde 55.2 under reductive amination conditions, to afford the aminoalkyl product 55.3. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product 55.3 is then hydrolyzed to yield the free carboxylic acid 55.4. The latter compound is then converted, as described above, into the aminoacid derivative 55.5.

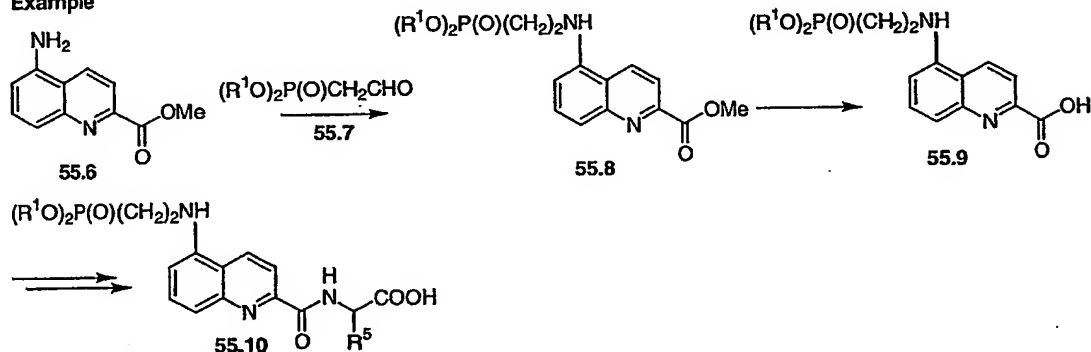
For example, methyl 7-aminoquinoline-2-carboxylate **55.6**, prepared as described in J. Am. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **55.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **55.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **55.9**. The latter compound is then converted, as described above, into the aminoacid derivative **55.10**. Using the above procedures, but employing, in place of the formylmethyl phosphonate **55.7**, different formylalkyl phosphonates **55.2**, and/or different aminoquinolines **55.1**, the corresponding products **55.5** are obtained.

Scheme 55

Method



Example



Preparation of phenylalanine derivatives 1.1 incorporating phosphonate moieties.

Scheme 56 illustrates the conversion of variously substituted phenylalanine derivatives **56.1** into epoxides **1.1**, the incorporation of which into the compounds **1** is depicted in Schemes **1** and **3**.

A number of compounds **56.1** or **56.2**, for example those in which X is 2, 3, or 4-OH, or X is 4-NH₂ are commercially available. The preparations of different compounds **56.1** or **56.2** are described in the literature. For example, the preparation of compounds **56.1** or **56.2** in which

X is 3-SH, 4-SH, 3-NH₂, 3-CH₂OH or 4-CH₂OH, are described respectively in WO0036136, J. Am. Chem. Soc., 1997, 119, 7173, Helv. Chim. Acta, 1978, 58, 1465, Acta Chem. Scand., 1977, B31, 109 and Syn. Com., 1998, 28, 4279. Resolution of compounds 56.1, if required, can be accomplished by conventional methods, for example as described in Recent Dev. Synth. Org. Chem., 1992, 2, 35.

The variously substituted aminoacids 56.2 are protected, for example by conversion to the BOC derivative 56.3, by treatment with BOC anhydride, as described in J. Med. Chem., 1998, 41, 1034. The product 56.3 is then converted into the methyl ester 56.4, for example by treatment with ethereal diazomethane. The substituent X in 56.4 is then transformed, using the methods described below, Schemes 57-59, into the group A. The products 56.5 are then converted, via the intermediates 56.6 - 56.9, into the epoxides 1.1. The methyl ester 56.5 is first hydrolyzed, for example by treatment with one molar equivalent of aqueous methanolic lithium hydroxide, or by enzymatic hydrolysis, using, for example, porcine liver esterase, to afford the carboxylic acid 56.6. The conversion of the carboxylic acid 56.6 into the epoxide 1.1, for example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, is then effected. The carboxylic acid is first converted into the acid chloride, for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone 56.7. The diazoketone is converted into the chloroketone 56.8 by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether. The latter compound is then reduced, for example by the use of sodium borohydride, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer 56.9 is separated by chromatography. This material is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide 1.1. Optionally, the above described series of reactions can be performed on the methyl ester 56.4, so as to yield the epoxide 1.1 in which A is OH, SH, NH, Nalkyl or CH₂OH.

Methods for the transformation of the compounds 56.4, in which X is a precursor group to the substituent link-P(O)(OR¹)₂, are illustrated in Schemes 57-59.

Scheme 56a illustrates the conversion of variously substituted phenylalanine derivatives 56a.1 into epoxides 3.1, the incorporation of which into the compounds 1 is depicted in Schemes 3. Starting from the same reagents described above, Scheme 56, the compound 56.2 is converted

into the epoxide **56a.6** as described in J. Org. Chem 1996,61, 3635. The amino acid **56.2** is converted to the tribenzyl ester **56a.3** by treatment with benzyl bromide in ethanol in the presence of potassium carbonate. The substituent X in **56a.3** is then transformed, using the methods described below, Schemes **57-59**, into the group A, compound **56a.4**. These methods describe procedures in which the amine is BOC protected. However the same procedures are applicable to other amine protecting groups such as dibenzyl. The products **56a.4** are then converted, via the intermediates **56a.5** into the epoxides **3.1**. The ester **56a.4** is reduced with lithium aluminum hydride to the alcohol which is then oxidized to the aldehyde **56a.4** by treatment with pyridine sulfur trioxide in DMSO and triethylamine. The aldehyde **56a.4** is then converted to the epoxide **3.1** by treatment with chloromethylbromide and excess lithium in THF at -65°C . A mixture of isomers are produced which are separated by chromatography.

Scheme **57** depicts the preparation of epoxides **57.4** incorporating a phosphonate group linked to the phenyl ring by means of a heteroatom O, S or N. In this procedure, the phenol, thiol, amine or carbinol **57.1** is reacted with a derivative of a dialkyl hydroxymethyl phosphonate **57.2**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is OH, SH, NH_2 or NHalkyl , an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is CH_2OH , a base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **57.3**, which, employing the sequence of reactions shown in Scheme **56** or **56a**, is transformed into the epoxide **57.4**.

For example, 2-tert.-butoxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid methyl ester, **57.5** (Fluka) is reacted with a dialkyl trifluoromethanesulfonyloxy phosphonate **57.6**, prepared as described in Tet. Lett., 1986, 27, 1477, in the presence of cesium carbonate, in dimethylformamide at ca 60° , to afford the ether product **57.5**. The latter compound is then converted, using the sequence of reactions shown in Scheme **56**, into the epoxide **57.8**.

Using the above procedures, but employing different phenols, thiols, amines and carbinols **57.1** in place of **57.5**, and/or different phosphonates **57.2**, the corresponding products **57.4** are obtained.

Scheme 58 illustrates the preparation of a phosphonate moiety is attached to the phenylalanine scaffold by means of a heteroatom and a multi-carbon chain.

In this procedure, a substituted phenylalanine derivative 58.1 is reacted with a dialkyl bromoalkyl phosphonate 58.2 to afford the product 58.3. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a suitable base such as sodium hydride or cesium carbonate. The product is then transformed, using the sequence of reactions shown in Scheme 56, into the epoxide 58.4.

For example, the protected aminoacid 58.5, prepared as described above (Scheme 56) from 3-mercaptophenylalanine, the preparation of which is described in WO 0036136, is reacted with a dialkyl 2-bromoethyl phosphonate 58.6, prepared as described in Synthesis, 1994, 9, 909, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the thioether product 58.7. The latter compound is then converted, using the sequence of reactions shown in Scheme 56, into the epoxide 58.8.

Using the above procedures, but employing different phenols, thiols, and amines 58.1 in place of 58.5, and/or different phosphonates 58.2, the corresponding products 58.4 are obtained.

Scheme 59 depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom.

In this procedure, a protected hydroxymethyl-substituted phenylalanine 59.1 is converted into the halomethyl-substituted compound 59.2. For example, the carbinol 59.1 is treated with triphenylphosphine and carbon tetrabromide, as described in J. Am. Chem. Soc., 108, 1035, 1986 to afford the product 59.2 in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate 59.3. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH₂ or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is OH, a strong base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester 59.4, which, employing the sequence of reactions shown in Scheme 56, is transformed into the epoxide 59.5.

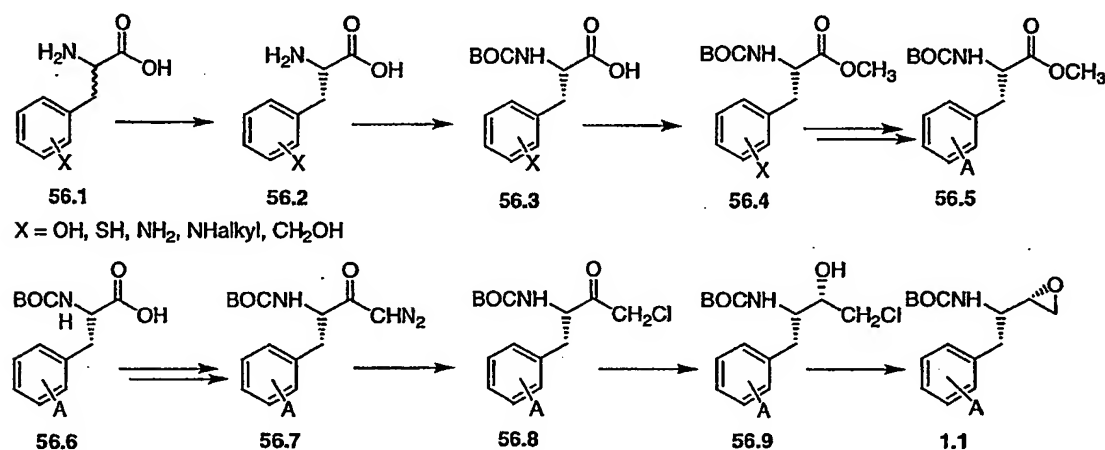
For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative 59.6, obtained from the 4-hydroxymethyl phenylalanine, the preparation of which is described in

Syn. Comm., 1998, 28, 4279, is converted into the bromo derivative **59.7**, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate **59.8**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product **59.9**. The latter

5 compound is then converted, using the sequence of reactions shown in Scheme 56, into the epoxide **59.10**.

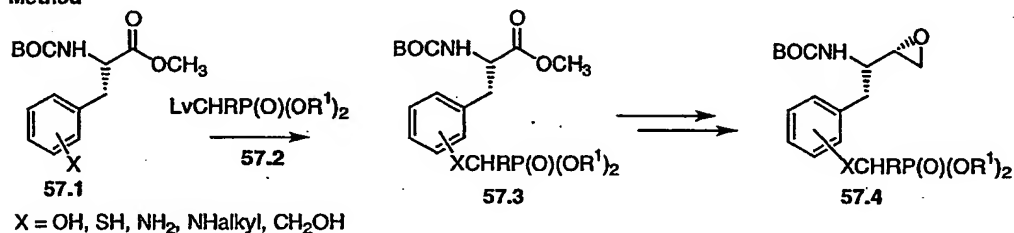
Using the above procedures, but employing different carbinols **59.1** in place of **59.6**, and/or different phosphonates **59.3**, the corresponding products **59.5** are obtained.

Scheme 56

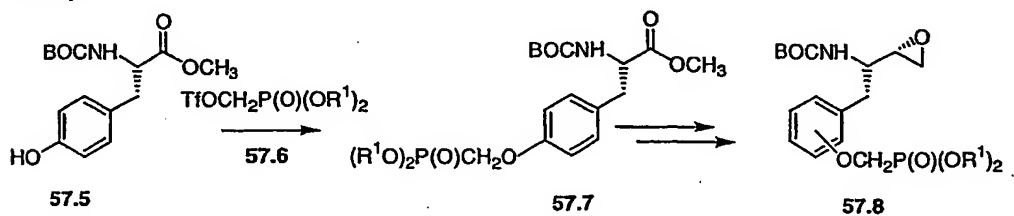


Scheme 57

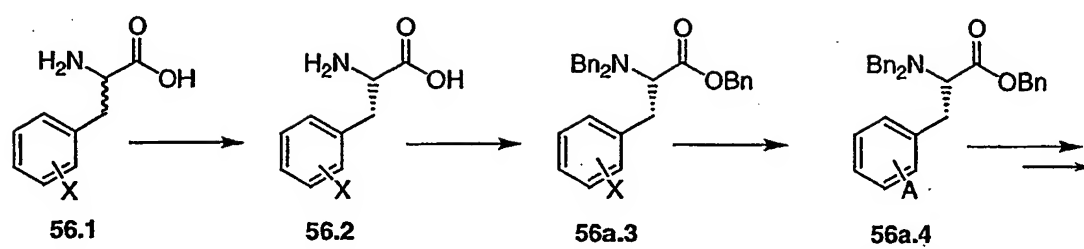
Method



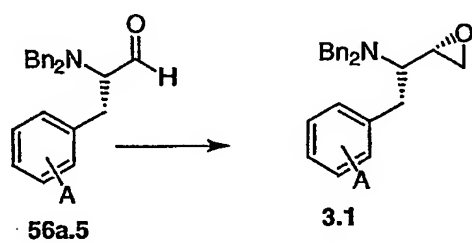
Example



Scheme 56a

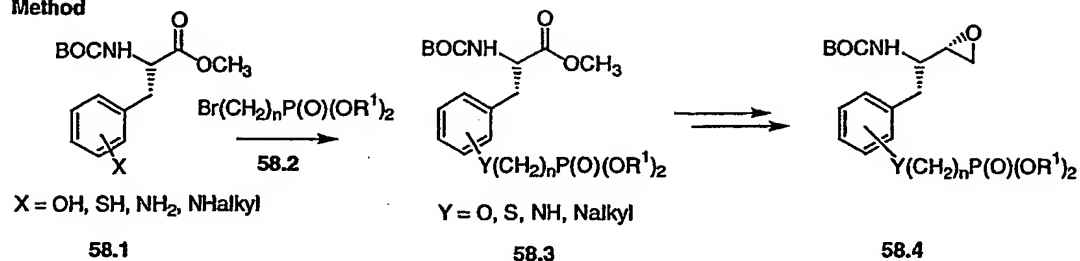


$X = OH, SH, NH_2, NHalkyl, CH_2OH$

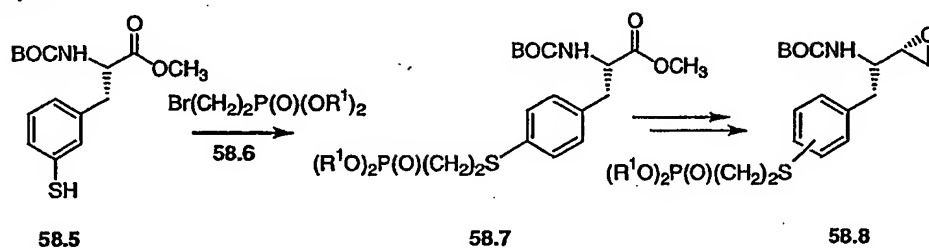


Scheme 58

Method

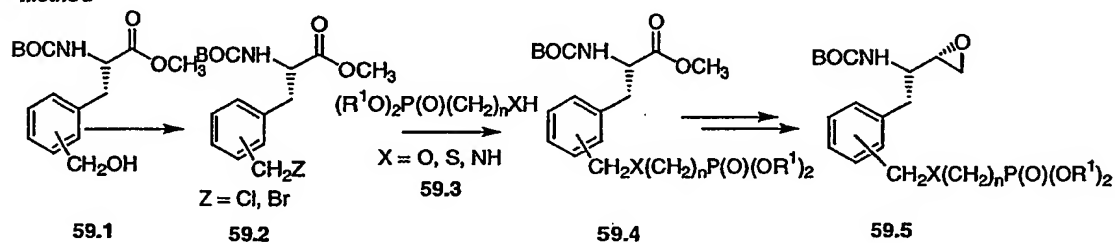


Example

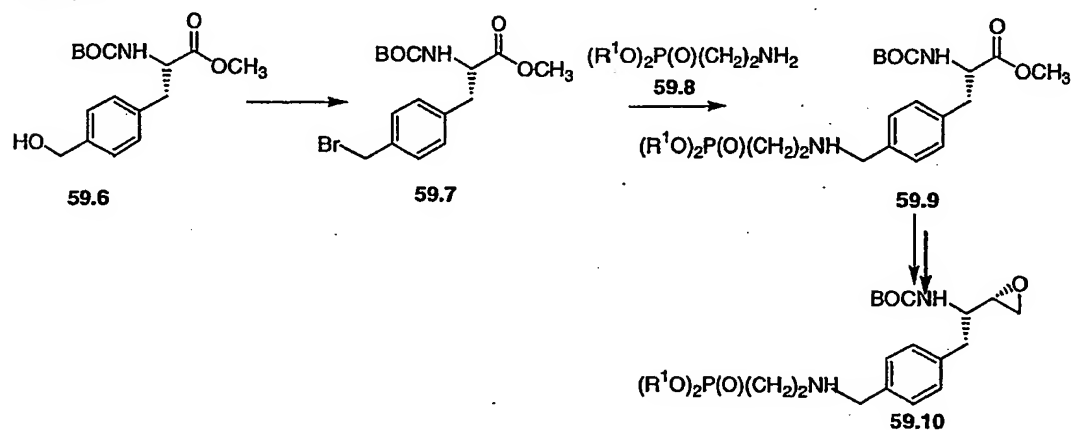


Scheme 59

Method



Example



Preparation of phenylalanine derivatives 2.1 incorporating phosphonate moieties or precursors thereto.

Scheme 60 illustrates the preparation of the hydroxymethyl oxazolidine derivative 2.1, in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor thereto, such as [OH], [SH] Br etc. In this reaction sequence, the substituted phenylalanine 60.1, in which A is as defined above, is transformed, via the intermediates 60.2 - 60.9, into the hydroxymethyl product 2.1. In this procedure, phenylalanine, or a substituted derivative thereof, 60.1, is converted into the phthalimido derivative 60.2. The conversion of amines into phthalimido derivatives is described, for example, in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 358. The amine is reacted with phthalic anhydride, 2-carboethoxybenzoyl chloride or N-carboethoxyphthalimide, optionally in the presence of a base such as triethylamine or sodium carbonate, to afford the protected amine 60.2. Preferably, the aminoacid is reacted with phthalic anhydride in toluene at reflux, to yield the phthalimido product. The carboxylic acid is then transformed into an activated derivative such as the acid chloride 60.3, in which X is Cl. The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of a tertiary amide such as dimethylformamide. Preferably, the carboxylic acid is transformed into the acid chloride by reaction with oxalyl chloride and a catalytic amount of dimethylformamide, in toluene solution at ambient temperature, as described in WO 9607642. The acid chloride 60.3, X = Cl, is then converted into the aldehyde 60.4 by means of a reduction reaction. This procedure is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 620. The transformation can be effected by means of catalytic hydrogenation, a procedure which is referred to as the Rosenmund reaction, or by chemical reduction employing, for example, sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride or triethylsilane. Preferably, the acid chloride 60.3 X = Cl, is hydrogenated in toluene solution over a 5% palladium on carbon catalyst, in the presence of butylene oxide, as described in WO 9607642, to afford the aldehyde 60.4. The aldehyde 60.4 is then transformed into the cyanohydrin derivative 60.5. The conversion of aldehydes into cyanohydrins is described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 211. For example, the aldehyde 60.4 is converted into the cyanohydrin 60.5 by reaction with trimethylsilyl cyanide in an inert solvent such as dichloromethane, followed by treatment with an organic acid such as citric acid, as described

in WO 9607642, or by alternative methods described therein. The cyanohydrin is then subjected to acidic hydrolysis, to effect conversion of the cyano group into the corresponding carboxy group, with concomitant hydrolysis of the phthalimido substituent to afford the aminoacid **60.6**. The hydrolysis reactions are effected by the use of aqueous mineral acid. For example, the substrate **60.5** is reacted with aqueous hydrochloric acid at reflux, as described in WO 9607642, to afford the carboxylic acid product **60.6**. The aminoacid is then converted into a carbamate, for example the ethyl carbamate **60.7**. The conversion of amines into carbamates is described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 317. The amine is reacted with a chloroformate, for example ethyl chloroformate, in the presence of a base such as potassium carbonate, to afford the carbamate **60.7**. For example, the aminoacid **60.6** is reacted, in aqueous solution, with ethyl chloroformate and sufficient aqueous sodium hydroxide to maintain a neutral pH, as described in WO 9607642, to afford the carbamate **60.7**. The latter compound is then transformed into the oxazolidinone **60.8**, for example by treatment with aqueous sodium hydroxide at ambient temperature, as described in WO 9607642. The resultant carboxylic acid is transformed into the methyl ester **60.9** by means of a conventional esterification reaction. The conversion of carboxylic acids into esters is described for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and an alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and an alkyl halide, for example an alkyl bromide. For example, the carboxylic acid **60.8** is converted into the methyl ester **60.9** by treatment with methanol at reflux temperature, in the presence of a catalytic amount of sulfuric acid, as described in WO 9607642. The carbomethoxyl group present in the compound **60.9** is then reduced to yield the corresponding carbinol **2.1**. The reduction of carboxylic esters to the carbinols is described in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 550. The transformation can be effected by the use of reducing agents such as borane-dimethylsulfide, lithium borohydride, diisobutyl aluminum hydride, lithium aluminum hydride and the like. For example, the ester **60.9** is reduced to the carbinol **2.1** by reaction with sodium borohydride in ethanol at ambient temperature, as described in WO 9607642.

The conversion of the substituent A into the group $\text{link-P(O)(OR}^1\text{)}_2$ may be effected at any convenient step in the reaction sequence, or after the reactant **2.1** has been incorporated into

the intermediates **1**. Specific examples of the preparation of the hydroxymethyl oxazolidinone reactant **2.1** are shown below, (Schemes **61-62**)

Scheme **61** depicts the preparation of hydroxymethyloxazolidinones **61.9** in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **61.1** is converted, using the series of reactions illustrated in Scheme **60**, into the bromophenyloxazolidinone **61.2**. The bromophenyl compound is then coupled, in the presence of a palladium (0) catalyst, with a dialkyl phosphite **61.3**, to afford the phosphonate product **61.4**. The reaction between aryl bromide and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, 56, 1981, and in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The carbomethoxy substituent in the resultant phosphonate ester **61.4** is then reduced with sodium borohydride to the corresponding hydroxymethyl derivative **61.5**, using the procedure described above (Scheme **60**)

For example, 3-bromophenylalanine **61.6**, prepared as described in Pept. Res., 1990, 3, 176, is converted, using the sequence of reactions shown in Scheme **60**, into 4-(3-bromo-benzyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester **61.7**. This compound is then coupled with a dialkyl phosphite **61.3**, in toluene solution at reflux, in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to afford the phosphonate ester **61.8**. The carbomethoxy substituent is then reduced with sodium borohydride, as described above, to afford the hydroxymethyl product **61.9**.

Using the above procedures, but employing, in place of 3-bromophenylalanine **61.6** different bromophenylalanines **61.1** and/or different dialkyl phosphites **61.3**, the corresponding products **61.5** are obtained.

Scheme **62** illustrates the preparation of phosphonate-containing hydroxymethyl oxazolidinones **62.9** and **62.12** in which the phosphonate group is attached by means of a heteroatom and a carbon chain. In this sequence of reactions, a hydroxy or thio-substituted phenylalanine **62.1** is converted into the benzyl ester **62.2** by means of a conventional acid catalyzed esterification reaction. The hydroxyl or mercapto group is then protected. The protection of phenyl hydroxyl and thiol groups are described, respectively, in Protective

Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in

5 Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The protected ester **62.3** is then reacted
10 with phthalic anhydride, as described above (Scheme 60) to afford the phthalimide **62.4**. The benzyl ester is then removed, for example by catalytic hydrogenation or by treatment with aqueous base, to afford the carboxylic acid **62.5**. This compound is transformed, by means of the series of reactions shown in Scheme 60, into the carbomethoxy oxazolidinone **62.6**, using in each step the same conditions as are described above (Scheme 60). The protected OH or
15 SH group is then deprotected. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into
20 the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978. The resultant phenol or thiol **62.7** is then reacted with a hydroxyalkyl phosphonate **62.20** under the conditions of the Mitsunobu reaction, as described above (Scheme 49), to afford the ether or thioether **62.8**. The latter compound is then reduced with sodium borohydride, as described
25 above (Scheme 60) to afford the hydroxymethyl analog **62.9**.

Alternatively, the phenol or thiophenol **62.7** is reacted with a dialkyl bromoalkyl phosphonate **62.10** to afford the alkylation product **62.11**. The alkylation reaction is performed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, optionally in the presence of potassium iodide, and in the presence of an inorganic base such as potassium or cesium
30 carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine. The ether or thioether product is then reduced with sodium borohydride to afford the hydroxymethyl compound **62.12**.

For example, 3-hydroxyphenylalanine **62.13** (Fluka) is converted in to the benzyl ester **62.14** by means of a conventional acid-catalyzed esterification reaction. The ester is then reacted with tert-butylchlorodimethylsilane and imidazole in dimethylformamide, to afford the silyl ether **62.15**. The protected ether is then reacted with phthalic anhydride, as described above
5 (Scheme **60**) to yield the phthalimido-protected compound **62.16**. Basic hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, then affords the carboxylic acid **62.17**. This compound is then transformed, by means of the series of reactions shown in Scheme **60**, into the carbomethoxy-substituted oxazolidinone **62.18**. The silyl protecting group is then removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient
10 temperature, to produce the phenol **62.19**. The latter compound is reacted with a dialkyl hydroxymethyl phosphonate **62.20** diethylazodicarboxylate and triphenylphosphine, by means of the Mitsunobu reaction. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and
15 R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React., 1992, 42, 335. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The reaction yields the phenolic ether **62.21**. The carbomethoxy group is then
20 reduced by reaction with sodium borohydride, as described above, to afford the carbinol **62.22**.

Using the above procedures, but employing, in place of 3-hydroxyphenylalanine **62.13**, different hydroxy or mercapto-substituted phenylalanines **62.1**, and/or different dialkyl hydroxyalkyl phosphonates **62.20**, the corresponding products **62.9** are obtained.

25 As a further example of the methods illustrated in Scheme **62**, 4-mercaptophenylalanine **62.23**, prepared as described in J. Am. Chem. Soc., 1997, 119, 7173, is converted into the benzyl ester **62.24** by means of a conventional acid-catalyzed esterification reaction. The mercapto group is then protected by conversion to the S-adamantyl group, by reaction with 1-adamantanol and trifluoroacetic acid at ambient temperature as described in Chem. Pharm.
30 Bull., 26, 1576, 1978. The amino group is then converted into the phthalimido group as described above, and the ester moiety is hydrolyzed with aqueous base to afford the carboxylic acid **62.27**. The latter compound is then transformed, by means of the series of reactions

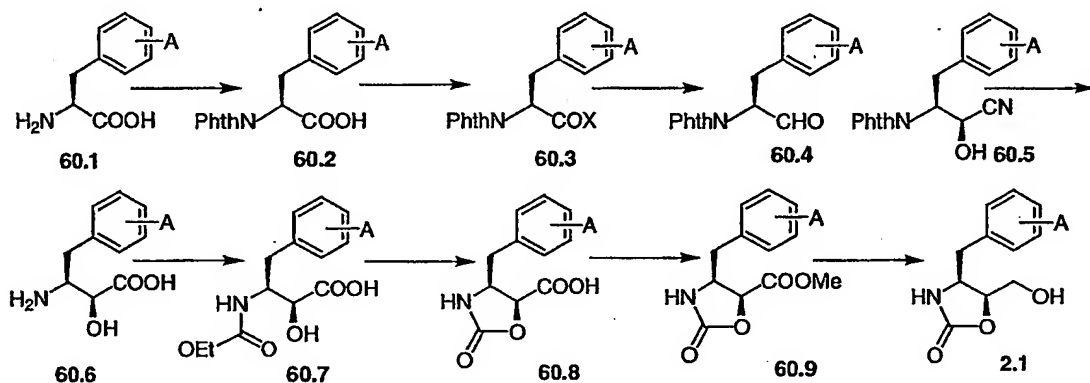
shown in Scheme 60, into the carbomethoxy oxazolidinone 62.28. The adamantyl protecting group is then removed by treatment of the thioether 62.28 with mercuric acetate in trifluoroacetic acid at 0°, as described in Chem. Pharm. Bull., 26, 1576, 1978, to produce the thiol 62.29. The thiol is then reacted with one molar equivalent of a dialkyl

- 5 bromoethylphosphonate 62.30, (Aldrich) and cesium carbonate in dimethylformamide at 70°, to afford the thioether product 62.31. The carbomethoxy group is then reduced with sodium borohydride, as described above, to prepare the carbinol 62.32.

Using the above procedures, but employing, in place of 4-mercaptophenylalanine 62.23, different hydroxy or mercapto-substituted phenylalanines 62.1, and/or different dialkyl

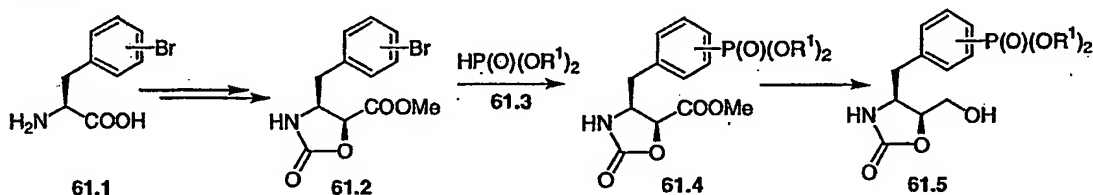
- 10 bromoalkyl phosphonates 62.10, the corresponding products 62.12 are obtained.

Scheme 60

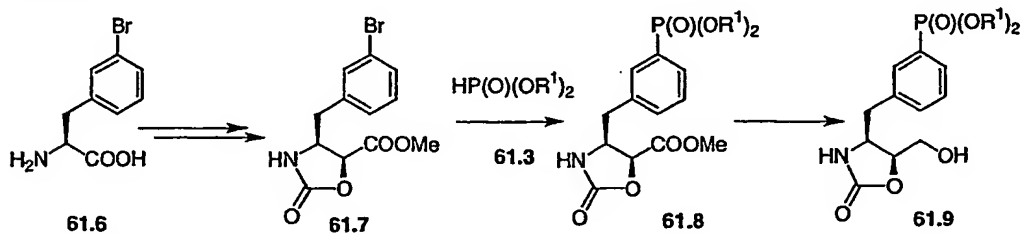


Scheme 61

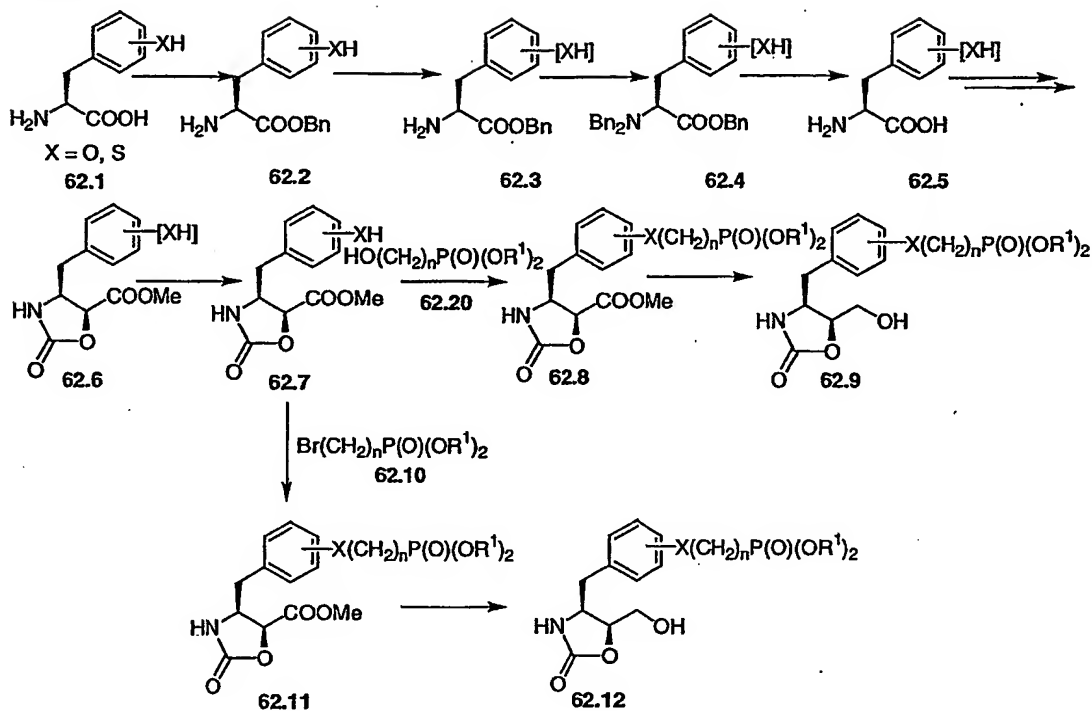
Method



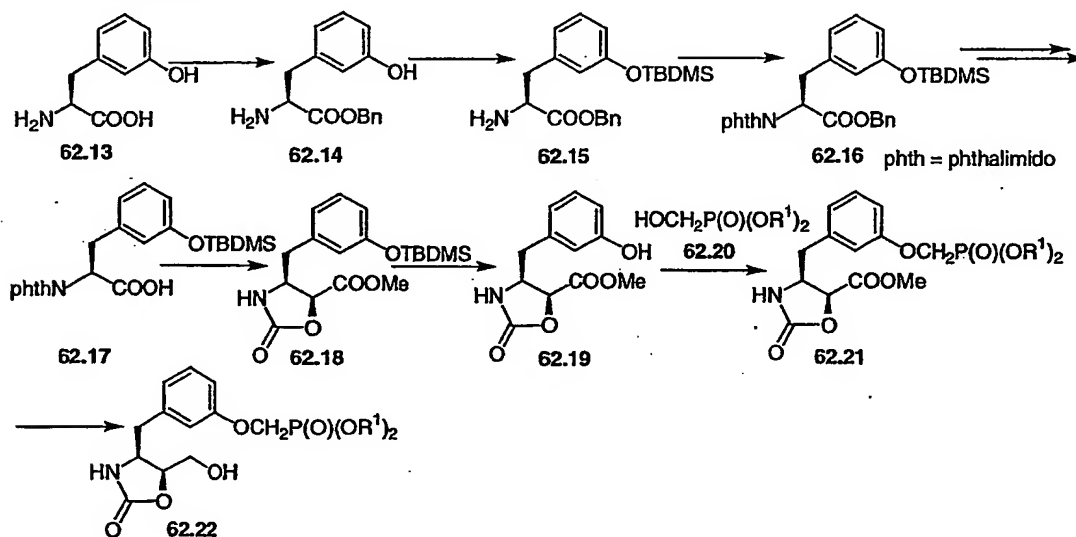
Example



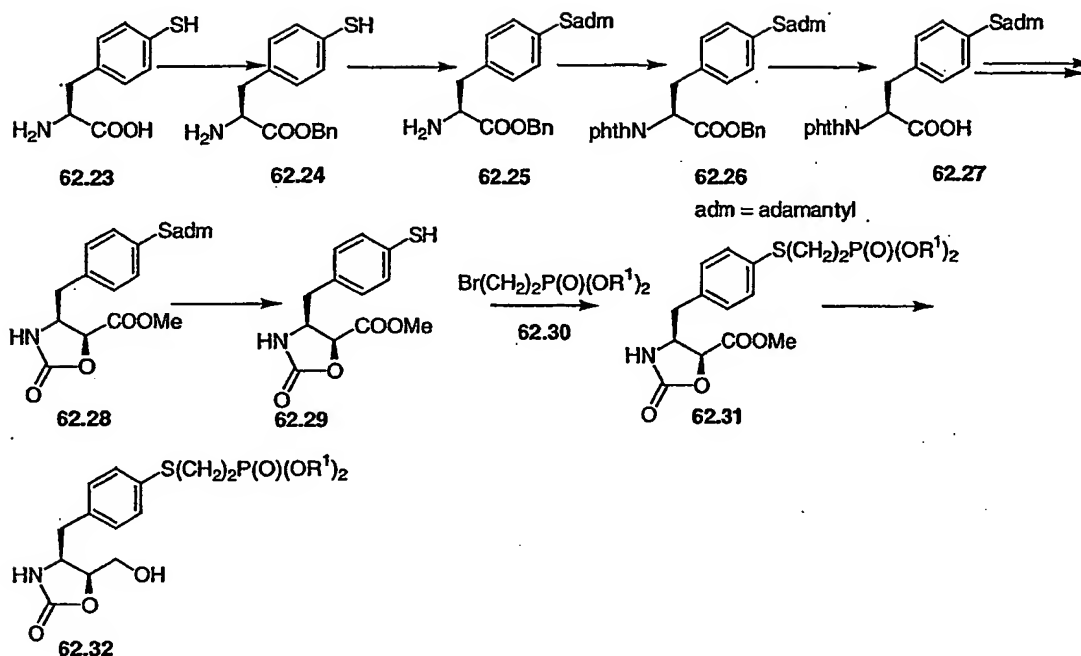
Scheme 62
Method



Scheme 62 Example 1



Scheme 62 Example 2



Preparation of the phosphonate-containing thiophenol derivatives 7.2.

- 5 Schemes 63 - 83 describe the preparation of phosphonate-containing thiophenol derivatives 7.2 which are employed as described above (Schemes 7 - 9) in the preparation of the phosphonate ester intermediates 1 in which X is sulfur.

- 10 Scheme 63 depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol 63.1 is protected to afford the product 63.2. The protection of phenyl thiol groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277. For example, thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a
- 15 chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in

Bull. Chem. Soc. Jpn., 37, 433, 1974. The product is then coupled, in the presence of triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, with a dialkyl phosphite 63.3, to afford the phosphonate ester 63.4. The thiol protecting group is then removed, as described above, to afford the thiol 63.5.

- 5 For example, 3-bromothiophenol 63.6 is converted into the 9-fluorenylmethyl (Fm) derivative 63.7 by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite 63.3, as described above, to afford the phosphonate ester 63.8. The Fm protecting group is then removed by treatment of the product with piperidine in
10 dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol 63.9.

Using the above procedures, but employing, in place of 3-bromothiophenol 63.6, different thiophenols 63.1, and/or different dialkyl phosphites 63.3, the corresponding products 63.5 are obtained.

15

- Scheme 64 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol 64.2 is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative 64.3. The latter compound is reacted
20 with a halodialkyl phosphite 64.4 to afford the product 64.5; deprotection then affords the thiophenol 64.6

- For example, 4-bromothiophenol 64.7 is converted into the S-triphenylmethyl (trityl) derivative 64.8, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative 64.9
25 by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorophosphite 64.10 to afford the phosphonate 64.11. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol 64.12.

- Using the above procedures, but employing, in place of the bromo compound 64.7, different
30 halo compounds 64.1, and/or different halo dialkyl phosphites 64.4, there are obtained the corresponding thiols 64.6.

Scheme 65 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol 65.1 is subjected to free-radical bromination to afford a bromomethyl product 65.2. This compound is reacted with a sodium dialkyl phosphite 65.3 or a trialkyl phosphite, to give the displacement or rearrangement product 65.4, which upon deprotection affords the thiophenol 65.5.

For example, 2-methylthiophenol 65.6 is protected by conversion to the benzoyl derivative 65.7, as described in *Protective Groups in Organic Synthesis*, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product 65.8. This material is reacted with a sodium dialkyl phosphite 65.3, as described in *J. Med. Chem.*, 35, 1371, 1992, to afford the product 65.9. Alternatively, the bromomethyl compound 65.8 is converted into the phosphonate 65.9 by means of the Arbuzov reaction, for example as described in *Handb. Organophosphorus Chem.*, 1992, 115. In this procedure, the bromomethyl compound 65.8 is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100° to produce the phosphonate 65.9. Deprotection of the phosphonate 65.9, for example by treatment with aqueous ammonia, as described in *J. Am. Chem. Soc.*, 85, 1337, 1963, then affords the thiol 65.10.

Using the above procedures, but employing, in place of the bromomethyl compound 65.8, different bromomethyl compounds 65.2, there are obtained the corresponding thiols 65.5.

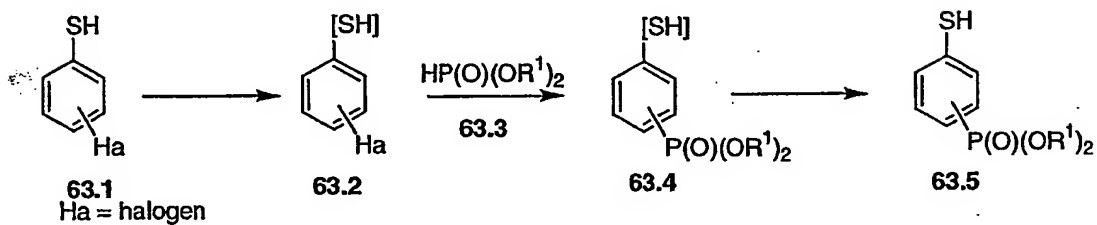
Scheme 66 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol 66.1 is reacted with a dialkyl hydroxyalkylphosphonate 66.2 under the conditions of the Mitsunobu reaction, for example as described in *Org. React.*, 1992, 42, 335, to afford the coupled product 66.3. Deprotection then yields the O- or S-linked products 66.4.

For example, the substrate 3-hydroxythiophenol, 66.5, is converted into the monotrityl ether 66.6, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate 66.7 in benzene, as described in *Synthesis*, 4, 327, 1998, to afford the ether compound 66.8. Removal of the trityl protecting group, as described above, then affords the thiophenol 66.9.

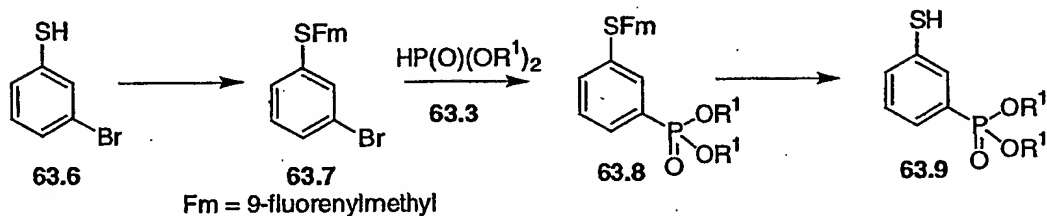
Using the above procedures, but employing, in place of the phenol 66.5, different phenols or thiophenols 66.1, there are obtained the corresponding thiols 66.4.

Scheme 63

Method



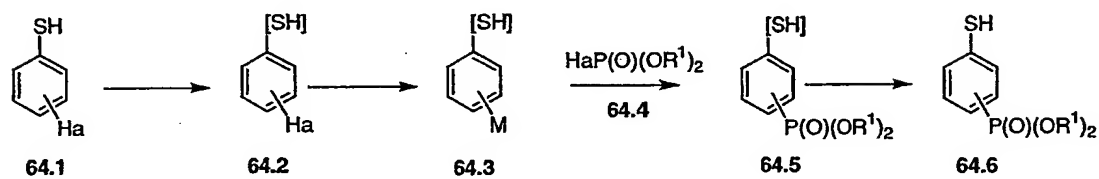
Example



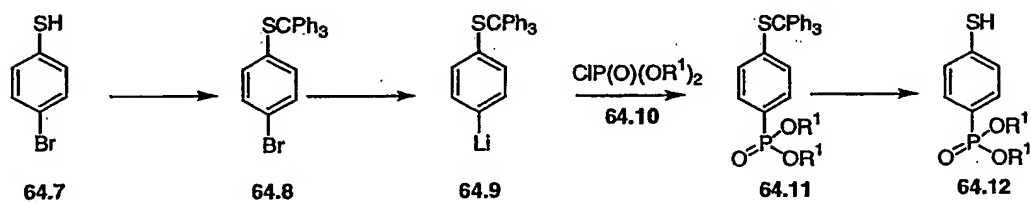
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Scheme 64

Method

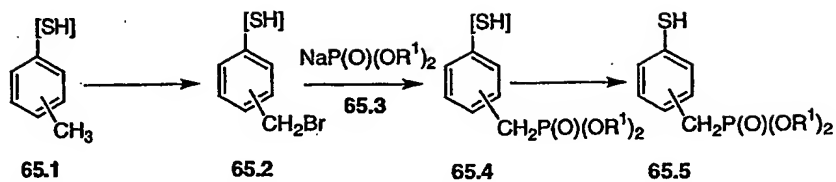


Example

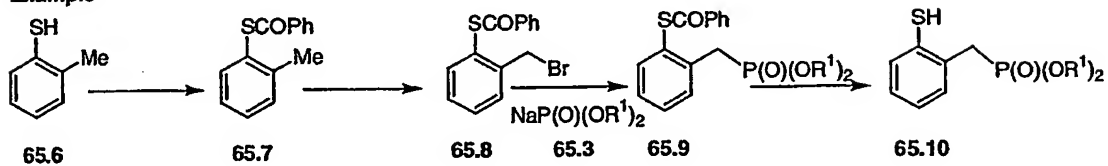


Scheme 65

Method

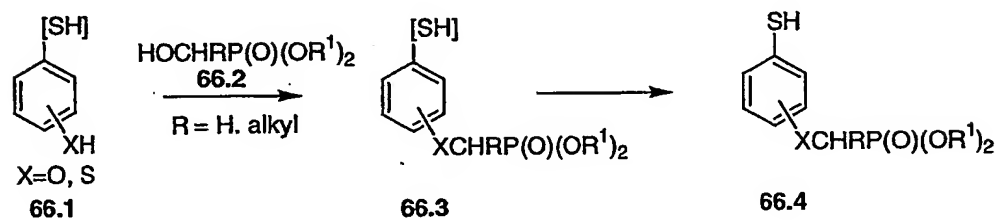


Example

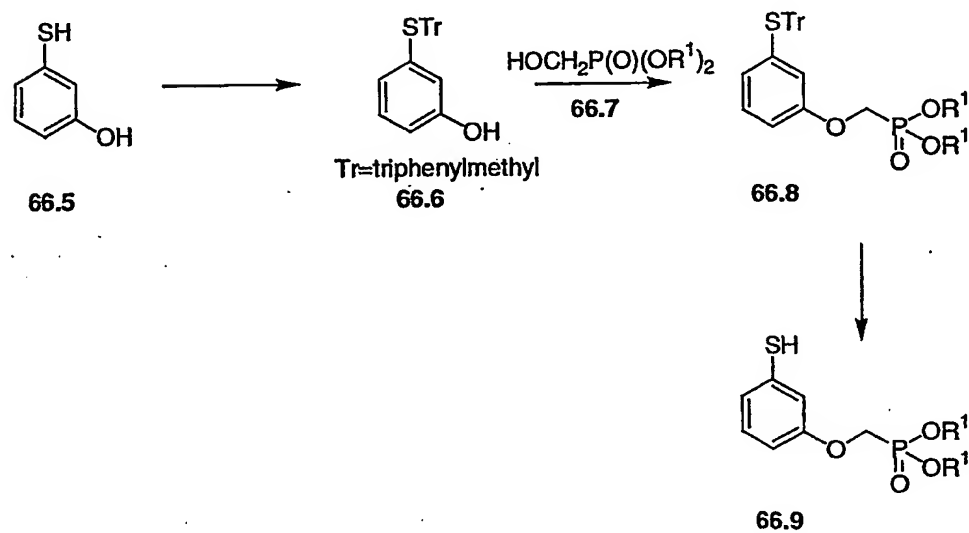


Scheme 66

Method



Example



Scheme 67 illustrates the preparation of thiophenols 67.4 bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol 67.1 is reacted with an activated ester, for example the trifluoromethanesulfonate 67.2, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product 67.3. Deprotection then affords the thiol 67.4.

For example, 4-methylaminothiophenol 67.5 is reacted in dichloromethane solution with one equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the S-acetyl product 67.6. This material is then reacted with a dialkyl trifluoromethanesulfonylmethyl phosphonate 67.7, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product 67.8. Preferably, equimolar amounts of the phosphonate 67.7 and the amine 67.6 are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product 67.8. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiophenol 67.9.

Using the above procedures, but employing, in place of the thioamine 67.5, different phenols, thiophenols or amines 67.1, and/or different phosphonates 67.2, there are obtained the corresponding products 67.4.

Scheme 68 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate 68.2. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol 68.1 is reacted with a dialkyl bromoalkyl phosphonate 68.2 to afford the product 68.3. Deprotection then affords the free thiophenol 68.4.

For example, 3-hydroxythiophenol 68.5 is converted into the S-trityl compound 68.6, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate 68.7, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of

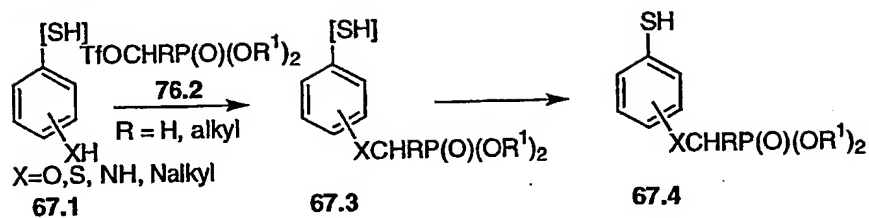
potassium iodide, at about 50°, to yield the ether product 68.8. Deprotection, as described above, then affords the thiol 68.9.

Using the above procedures, but employing, in place of the phenol 68.5, different phenols, thiophenols or amines 68.1, and/or different phosphonates 68.2, there are obtained the
5 corresponding products 68.4.

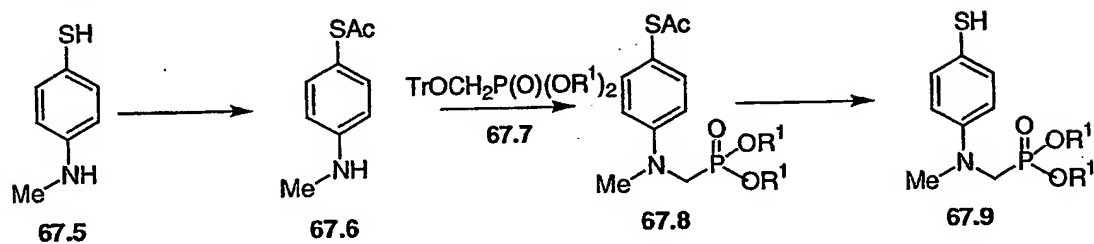
Scheme 69 depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 69.2 is
10 coupled with an aromatic bromo compound 69.1. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as
15 tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product 69.3. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate 69.4, or the saturated analog 69.6.
20 For example, 3-bromothiophenol is converted into the S-Fm derivative 69.7, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate 69.8, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar
25 solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product 69.9. Deprotection, as described above, then affords the thiol 69.10. Optionally, the initially formed unsaturated phosphonate 69.9 is subjected to reduction, for example using diimide, as described above, to yield the saturated product 69.11, which upon deprotection affords the thiol 69.12.
30 Using the above procedures, but employing, in place of the bromo compound 69.7, different bromo compounds 69.1, and/or different phosphonates 69.2, there are obtained the corresponding products 69.4 and 69.6

Scheme 67

Method

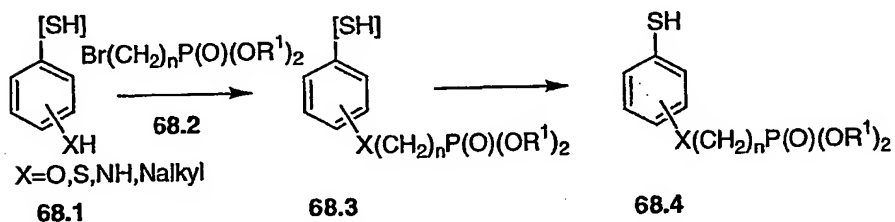


Example

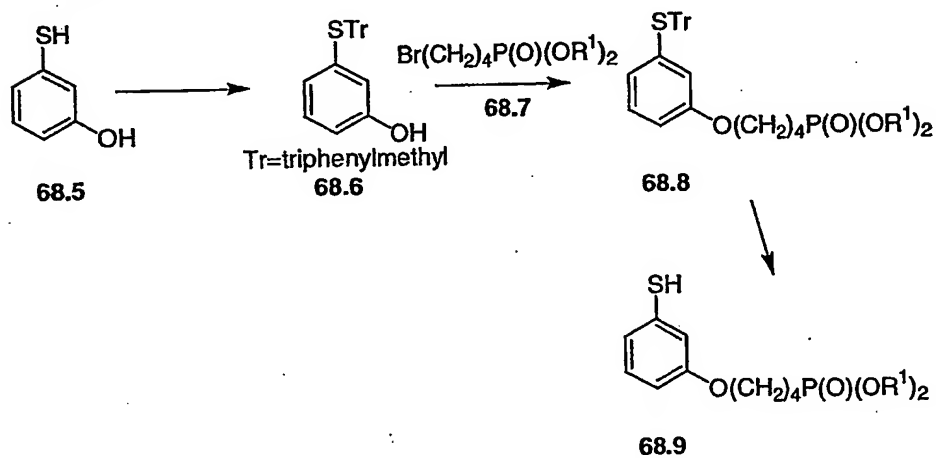


Scheme 68

Method

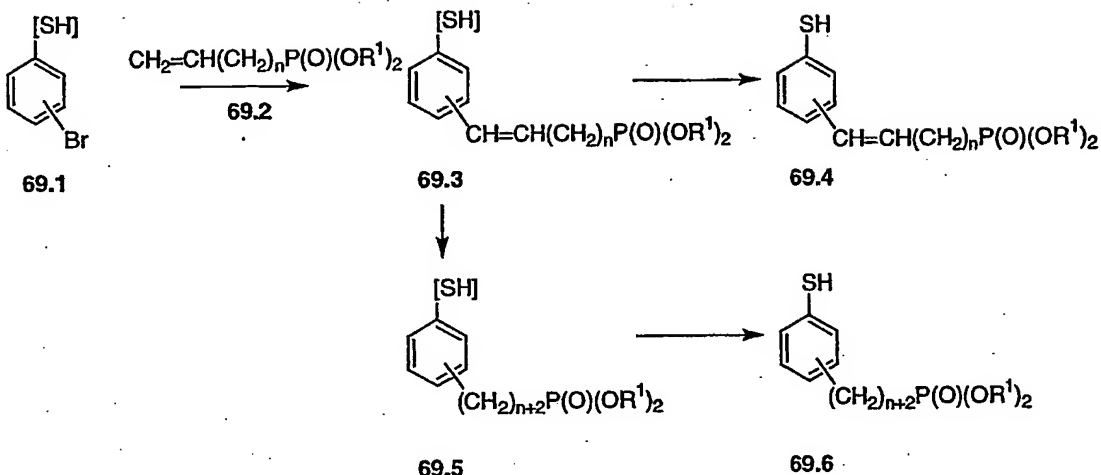


Example

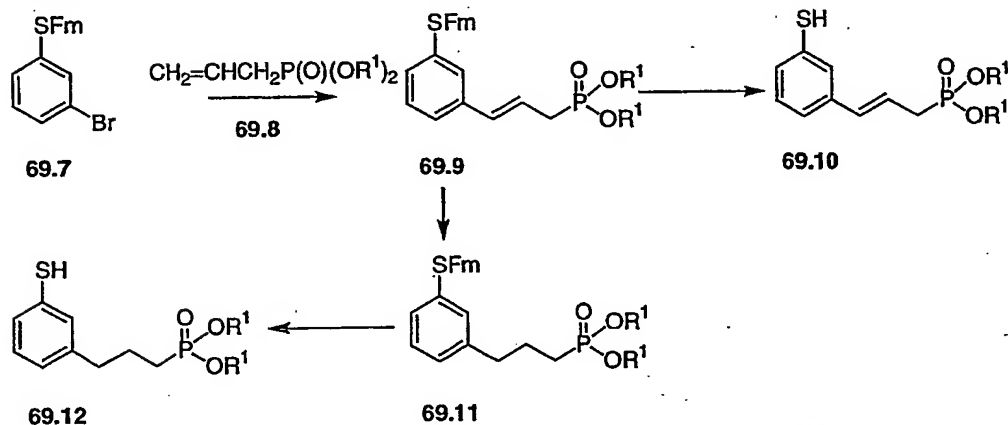


Scheme 69

Method



Example



Scheme 70 illustrates the preparation of an aryl-linked phosphonate ester 70.4 by means of a
 5 palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a
 phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock,
 VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid 70.1 is obtained by means of a
 metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for
 example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the
 10 diaryl product 70.3 which is deprotected to yield the thiol 70.4.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane,
 in the presence of a base such as imidazole, as described in Protective Groups in Organic

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **70.5**. This material is reacted with a dialkyl 4-bromophenylphosphonate **70.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **70.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **70.8**.

Using the above procedures, but employing, in place of the boronate **70.5**, different boronates **70.1**, and/or different phosphonates **70.2**, there are obtained the corresponding products **70.4**.

- 10 Scheme **71** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **71.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **71.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **71.3** is then deprotected to afford the thiol **71.4**. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **71.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **71.5** is then reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, **71.6**, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The thioether product **71.7** thus obtained is deprotected, as described above, to afford the thiol **71.8**.

- 25 Using the above procedures, but employing, in place of the thiophenol **71.5**, different phenols, thiophenols or amines **71.1**, and/or different phosphonates **71.2**, there are obtained the corresponding products **71.4**.

Scheme **72** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

- 30 In this procedure, a suitably protected thiophenol **72.1**, for example an indoline (in which X-Y is (CH₂)₂), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is (CH₂)₃) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **72.2**, in the presence of an

organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester 72.3. Deprotection, as described above, then affords the thiol 72.4. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding

5 hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in

10 J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p 707.

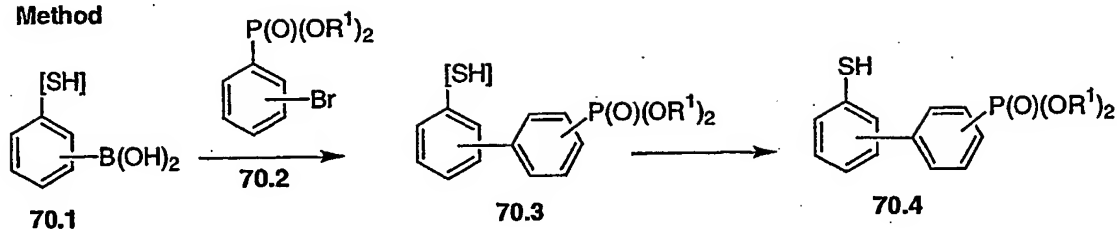
15 For example, 2,3-dihydro-1H-indole-5-thiol, 72.5, the preparation of which is described in EP 209751, is converted into the benzoyl ester 72.6, as described above, and the ester is then reacted with the trifluoromethanesulfonate 72.7, in a polar organic solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, to yield the phosphonate 72.8. Deprotection, for example by reaction with dilute aqueous ammonia, as

20 described above, then affords the thiol 72.9.

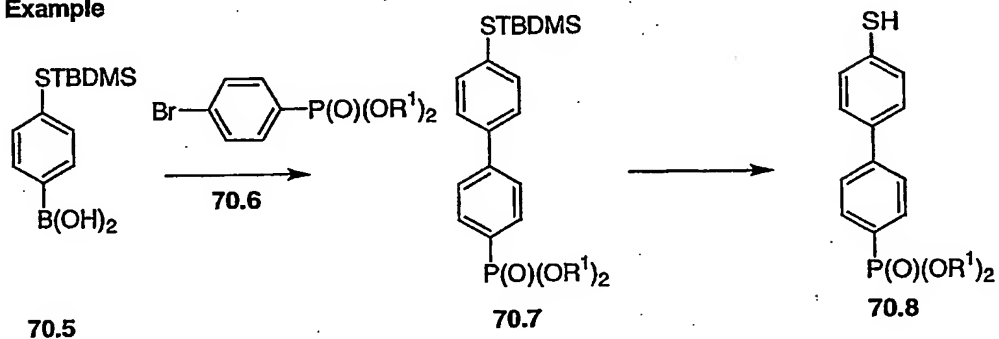
Using the above procedures, but employing, in place of the thiol 72.5, different thiols 72.1, and/or different triflates 72.2, there are obtained the corresponding products 72.4.

Scheme 70

Method

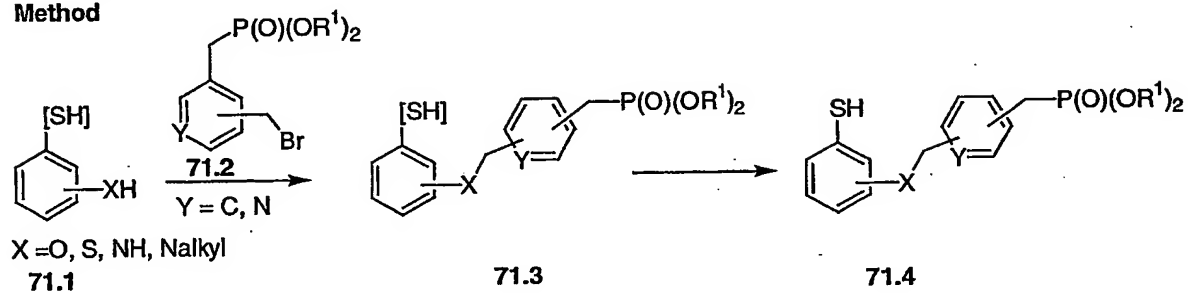


Example

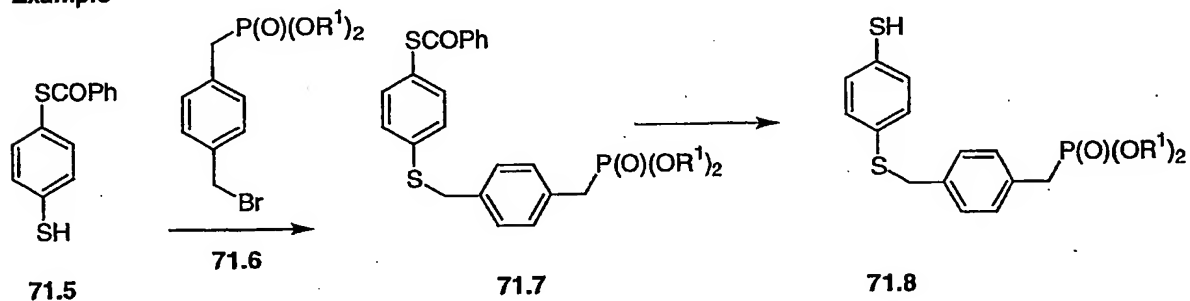


Scheme 71

Method



Example



5 Preparation of phosphonate-containing analogs of isobutylamine 10.2.

Schemes 73 - 75 illustrate the preparation of the phosphonate-containing analogs of isobutylamine which are employed in the preparation of the phosphonate esters 2.

Scheme 73 depicts the preparation of phosphonates which are attached to the isobutylamine by means of an amide linkage. In this procedure, an aminoacid 73.1 is protected to afford the product 73.2. The protection of amino groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, 309. Amino groups are protected, for example, by conversion into carbamates such as the tert. butoxycarbonate (BOC) derivative, or by reaction with phthalic anhydride to afford the phthalimido (phth) derivative. The amine-protected aminoacid 73.2 is then coupled with a dialkyl aminoalkyl phosphonate 73.3, to yield the amide 73.4. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide. Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The protecting group is then removed to afford the amine 73.5. Deprotection of amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 309ff. For example, BOC groups are removed by treatment with acids such as trifluoroacetic acid, and phthalimido groups are removed by reaction with hydrazine hydrate. For example, 2-methyl-4-aminobutyric acid 73.6 (Acros) is reacted with phthalic anhydride in refluxing toluene, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 358; to give the phthalimido derivative 73.7. The product is coupled with a dialkyl aminoethyl phosphonate 73.8, the preparation of which is described in J. Org. Chem., 2000, 65, 676,

in the presence of dicyclohexyl carbodiimide, to give the amide 73.9. The protecting group is removed by reaction of the product with ethanolic hydrazine at ambient temperature, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 358, to afford the amine 73.10.

- 5 Using the above procedures, but employing, in place of the acid 73.6, different acids 73.1, and/or different amines 73.3, the corresponding amides 73.5 are obtained.

Scheme 74 depicts the preparation of isobutylamine phosphonates in which the phosphonate is attached by means of an aromatic ring. In this procedure, 2-methyl-but-3-enylamine 74.1, prepared as described in Org. Prep. Proc. Int. 1976, 8, 75, is coupled, in the presence of a palladium catalyst, as described above (Scheme 50) with a dialkyl bromophenyl phosphonate 74.2 to afford the olefinic product 74.3. Optionally, the product is reduced to afford the saturated analog 74.4. The reduction is effected catalytically, for example by the use of a palladium catalyst, or chemically, for example by the use of diimide.

- 10 For example, the amine 74.1 is coupled with a dialkyl 4-bromophenyl phosphonate 74.5, prepared as described in J. Organomet. Chem., 1999, 581, 62, to yield the product 74.6. Catalytic hydrogenation in ethanol, using a 5% palladium catalyst, then affords the saturated compound 74.7.

- Using the above procedures, but employing, in place of the phosphonate 74.5, different phosphonates 74.2 the corresponding products 74.3 and 74.4 are obtained.

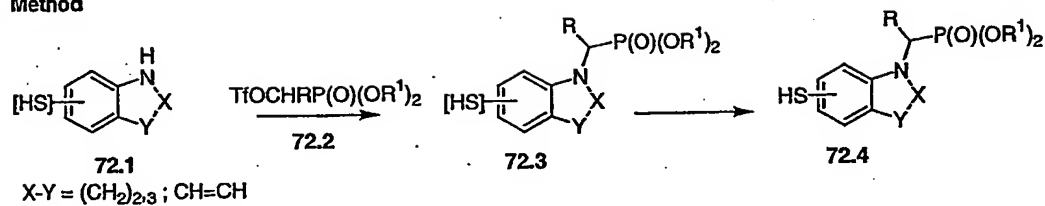
Scheme 75 illustrates the preparation of isobutylamine phosphonates in which the phosphonate group is attached by means of an alkylene chain. In this procedure, a bromoamine 75.1 is protected, as described in Scheme 73, to afford the derivative 75.2. The product is then reacted with a trialkyl phosphite 75.3, in an Arbuzov reaction, as described in Scheme 65, to give the phosphonate 75.4. Deprotection then affords the amine 75.5.

- For example, 4-bromo-2-methyl-butylamine 75.6, prepared as described in Tet., 1998, 54, 2365, is converted, as described above, into the phthalimido derivative 75.7. The product is then heated at 110° with a trialkyl phosphite 75.3 to yield the phosphonate 75.8, which upon reaction with ethanolic hydrazine affords the amine 75.9.

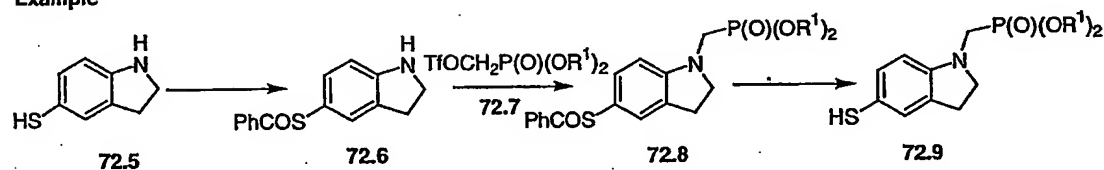
Using the above procedures, but employing, in place of the bromide 75.6, different bromides 75.1, and/or different phosphites 75.3, the corresponding products 75.5 are obtained.

Scheme 72

Method

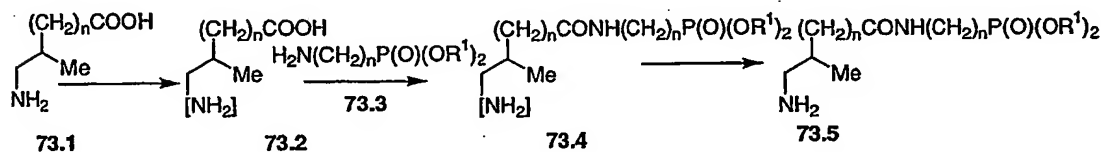


Example

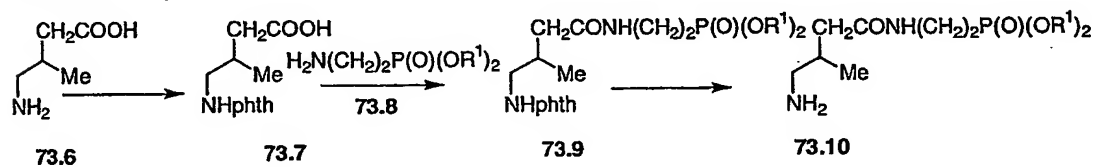


Scheme 73

Method

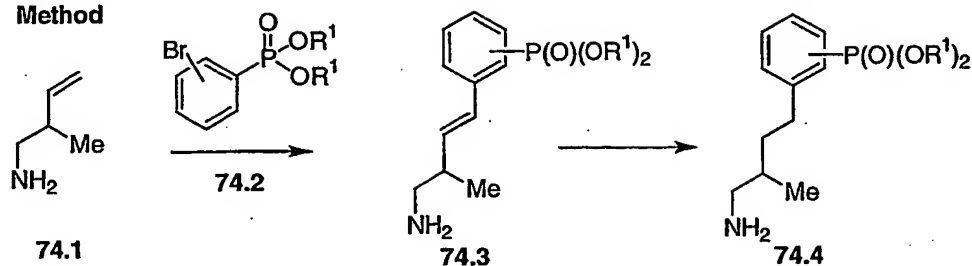


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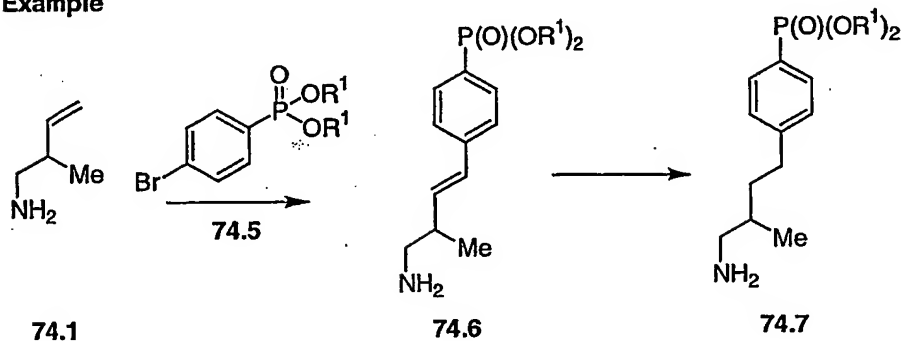


Scheme 74

Method

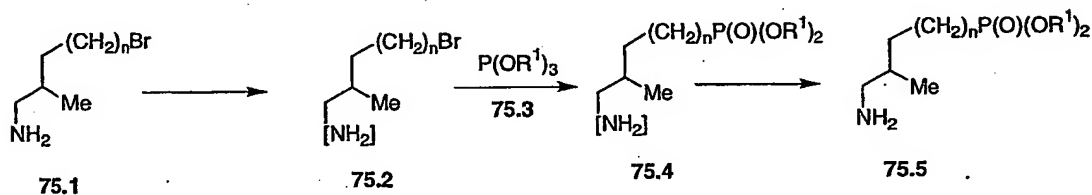


Example

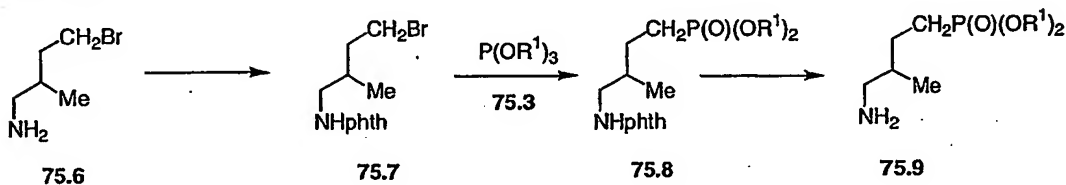


Scheme 75

Method



Example



Preparation of cyclopentylmethylamine phosphonates.

5

Schemes 76 - 78 illustrate the preparation of cyclopentylmethylamine phosphonates which are employed, as shown in Schemes 10 - 12, in the preparation of the phosphonate esters 3.

Scheme 76 depicts the preparation of phosphonates attached to the cyclopentyl ring either directly or by means of an alkoxy link. In this procedure, a hydroxy-substituted

10

- cyclopentylmethylamine **76.1** is protected, and the protected derivative **76.2** is converted into the corresponding bromide **76.3**, for example by treatment with carbon tetrabromide and triphenyl phosphine as described in Scheme 59. The bromo compound is then reacted with a trialkyl phosphite **76.4** in an Arbuzov reaction, as described above, to afford the phosphonate **76.5** which is then deprotected to give the amine **76.6**. Alternatively, the protected amine **76.2** is reacted with a dialkyl bromoalkyl phosphonate **76.7** to give the ether **76.8**. The alkylation reaction is conducted at ca 100° in a polar organic solvent such as dimethylformamide in the presence of a base such as sodium hydride or lithium hexamethyl disilylazide. The product is then deprotected to give the amine **76.9**.
- 10 For example, 3-aminomethyl-cyclopentanol **76.10**, prepared as described in Tet., 1999, 55, 10815, is converted, as described above, into the phthalimido derivative **76.11**. The product is then converted, as described above, into the bromo analog **76.12**. The latter compound is reacted at ca 120° with a trialkyl phosphite **76.4** to afford the phosphonate **76.13**, which upon deprotection by reaction with hydrazine yields the amine **76.14**.
- 15 Using the above procedures, but employing, in place of the bromide **76.12**, different bromides **76.3**, and/or different phosphites **76.4**, the corresponding products **76.6** are obtained. Alternatively, 2-aminomethyl-cyclopentanol **76.15**, prepared as described in Tet., 1999, 55, 10815, is converted into the phthalimido derivative **76.16**. The product is then reacted in dimethylformamide solution with an equimolar amount of a dialkyl bromopropyl phosphonate **76.17**, prepared as described in J. Am. Chem. Soc., 2000, 122, 1554, and sodium hydride, to give the ether **76.18**. Deprotection, as described above, then affords the amine **76.19**.
- 20 Using the above procedures, but employing, in place of the carbinol **76.15**, different carbinols **76.1**, and/or different phosphonates **76.7**, the corresponding products **76.9** are obtained.
- 25 Scheme 77 illustrates the preparation of cyclopentylmethylenamines in which the phosphonate group is attached by means of an amide group. In this procedure, a carboxyalkyl-substituted cyclopentylmethylamine **77.1** is protected to afford the derivative **77.2**. The product is then coupled, as described above, (Scheme 1) with a dialkyl aminoalkyl phosphonate **77.3** to yield the amide **77.4**. Deprotection then affords the amine **77.5**.
- 30 For example, 3-aminomethyl-cyclopentanecarboxylic acid **77.6** prepared as described in J. Chem. Soc. Perkin 2, 1995, 1381, is converted into the BOC derivative **77.7**, by reaction with BOC anhydride in aqueous sodium hydroxide, as described in Proc. Nat. Acad. Sci., 69, 730,

1972. The product is then coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminopropyl phosphonate 77.8 to produce the amide 77.9. Removal of the BOC group, for example by treatment with hydrogen chloride in ethyl acetate, then affords the amine 77.10. Using the above procedures, but employing, in place of the carboxylic acid 77.6, different
5 carboxylic acids 77.1, and/or different phosphonates 77.3, the corresponding products 77.5 are obtained.

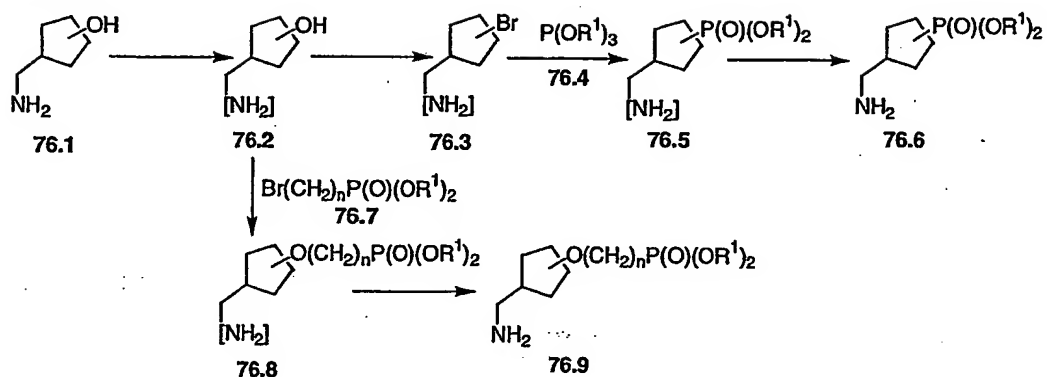
Scheme 78 illustrates the preparation of cyclopentylmethyamines in which the phosphonate group is attached by means of an aminoalkyl group. In this procedure, the more reactive amino
10 group of an amino-substituted cyclopentylmethyamine 78.1 is protected, to give the derivative 78.2. The product is then coupled, by means of a reductive amination reaction, as described in Scheme 55, with a dialkyl formylalkyl phosphonate 78.3 to give the amine product 78.4, which upon deprotection affords the amine 78.5.

For example, 2-aminomethyl-cyclopentylamine 78.6 prepared as described in WO 9811052, is
15 reacted with one molar equivalent of phthalic anhydride in refluxing tetrahydrofuran, to yield the phthalimido derivative 78.7. The latter compound is reacted, in the presence of sodium cyanoborohydride, with a dialkyl formylmethyl phosphonate 78.8, prepared as described in Zh. Obschei. Khim., 1987, 57, 2793, to afford the product 78.9. Deprotection, as described above, then yields the amine 78.10.

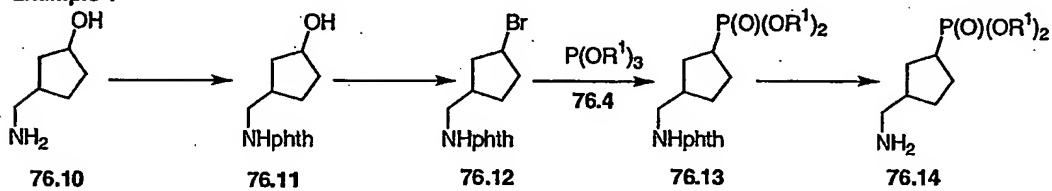
20 Using the above procedures, but employing, in place of the diamine 78.6, different diamines 78.1, and/or different phosphonates 78.3, the corresponding products 78.5 are obtained.

Scheme 76

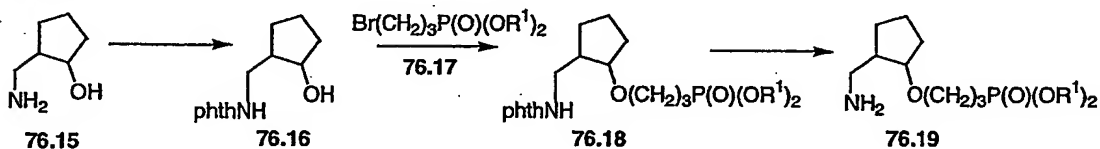
Method



Example 1

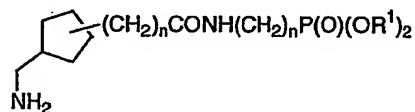
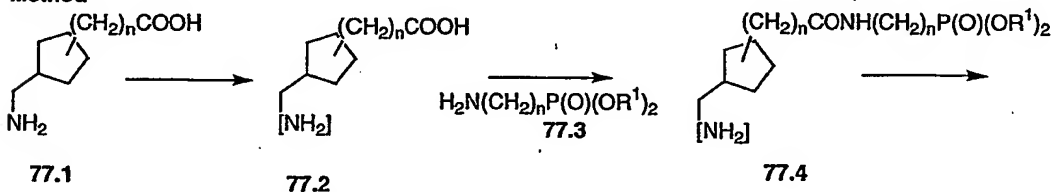


Example 2



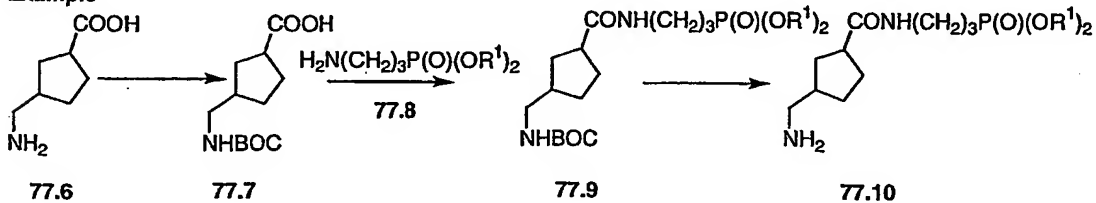
Scheme 77

Method



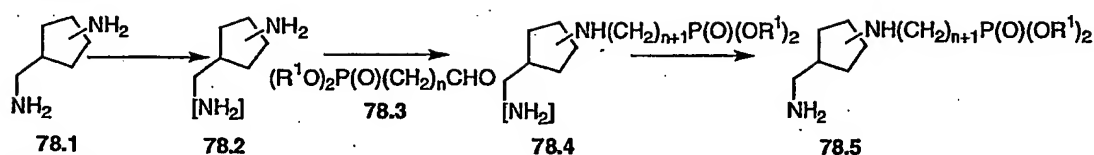
77.5

Example

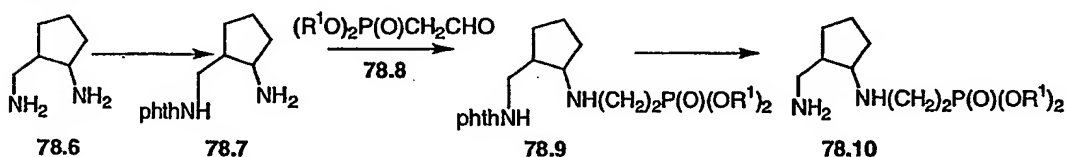


Scheme 78

Method



Example



Preparation of phosphonate-substituted fluorobenzylamines 39.2.

5

Schemes 79 and 80 illustrate the preparation of phosphonate-substituted 3-fluorobenzylamines 39.2 which are used in the preparation of the phosphonate esters 6.

Scheme 79 depicts the preparation of fluorobenzylamines in which the phosphonate is attached by means of an amide or aminoalkyl linkage. In this procedure, the more reactive amino group in an amino-substituted 3-fluorobenzylamine 79.1 is protected. The product 79.2 is then coupled with a dialkyl carboxyalkyl phosphonate 79.3 to give the amide 79.4, which upon deprotection yields the free amine 79.5. Alternatively, the mono-protected diamine 79.2 is coupled, under reductive amination conditions, with a dialkyl formylalkyl phosphonate 79.6, to produce the amine 79.7, which upon deprotection affords the benzylamine 79.8.

For example, 4-amino-3-fluorobenzylamine 79.9, prepared as described in WO 9417035, is reacted in pyridine solution with one molar equivalent of acetic anhydride, to give the acetylamino product 79.10. The product is reacted with a dialkyl carboxyethyl phosphonate 79.11, (Epsilon) and dicyclohexyl carbodiimide, to afford the amide 79.12. Deprotection, for example by reaction with 85% hydrazine, as described in J. Org. Chem., 43, 4593, 1978, then gives the amine 79.13.

Using the above procedures, but employing, in place of the diamine 79.9, different diamines 79.1, and/or different phosphonates 79.3, the corresponding products 79.5 are obtained. As a further example, the mono-protected diamine 79.10 is reacted, as described above, with a dialkyl formyl phosphonate 79.13, (Aurora) and sodium cyanoborohydride, to give the amination product 79.14. Deprotection then affords the amine 79.15.

Using the above procedures, but employing, in place of the diamine 79.10 different diamines 79.2, and/or different phosphonates 79.6, the corresponding products 79.8 are obtained.

Scheme 80 depicts the preparation of fluorobenzylamines in which the phosphonate is attached either directly or by means of a saturated or unsaturated alkylene linkage. In this procedure, a bromo-substituted 3-fluorobenzylamine 80.1 is protected. The product 80.2 is coupled, by means of a palladium-catalyzed Heck reaction, as described in Scheme 50, with a dialkyl alkenyl phosphonate 80.3, to give the olefinic product 80.4 which upon deprotection affords the amine 80.5. Optionally, the double bond is reduced, for example by catalytic hydrogenation over a palladium catalyst, to yield the saturated analog 80.9. Alternatively, the protected bromobenzylamine 80.6 is coupled, as described in Scheme 61, in the presence of a palladium catalyst, with a dialkyl phosphite 80.6 to produce the phosphonate 80.7.

Deprotection then affords the amine 80.8.

For example, 2-bromo-5-fluorobenzylamine 80.10, (Esprix Fine Chemicals) is converted, as described above, into the N-acetyl derivative 80.11. The product is then coupled in dimethylformamide solution with a dialkyl vinyl phosphonate 80.12, (Fluka) in the presence of palladium (II) acetate and triethylamine, to give the coupled product 80.13. Deprotection then affords the amine 80.14 and hydrogenation of the latter compound yields the saturated analog 80.15.

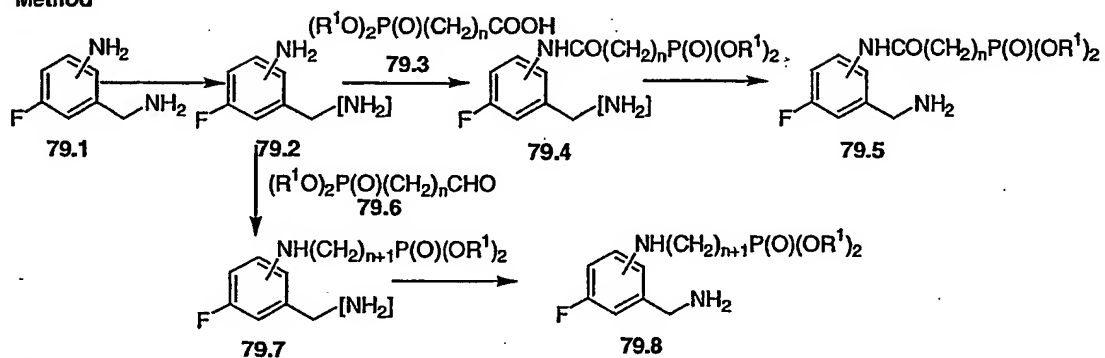
Using the above procedures, but employing, in place of the bromo compound 80.10 different bromo compounds 80.1, and/or different phosphonates 80.3, the corresponding products 80.5 and 80.9 are obtained.

As a further example, the protected amine 80.11 is coupled, in toluene at 100°, with a dialkyl phosphite 80.6, in the presence of tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine, to give the phosphonate 80.16. Deprotection then affords the amine 80.17.

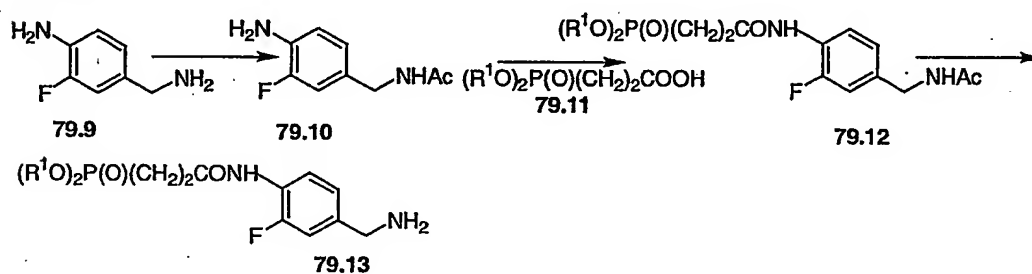
Using the above procedures, but employing, in place of the bromo compound 80.11 different bromo compounds 80.2, and/or different phosphites 80.6, the corresponding products 80.8 are obtained.

Scheme 79

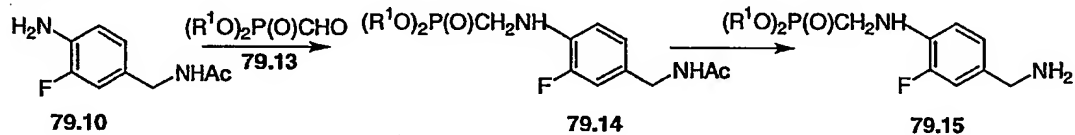
Method



Example 1

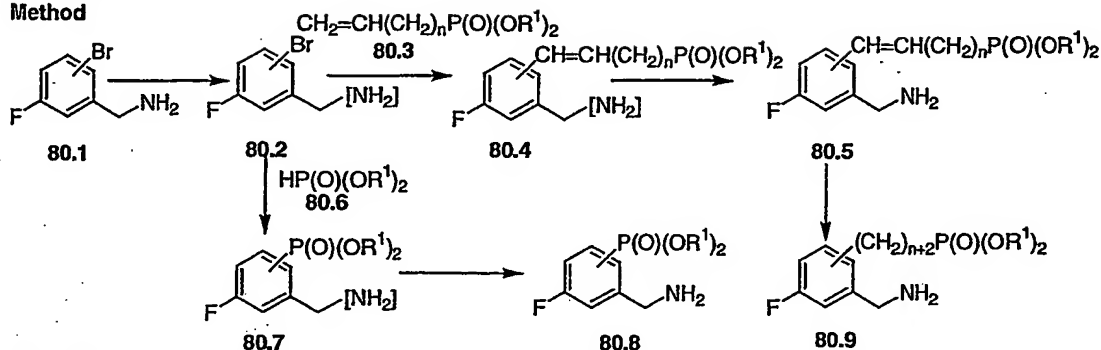


Example 2

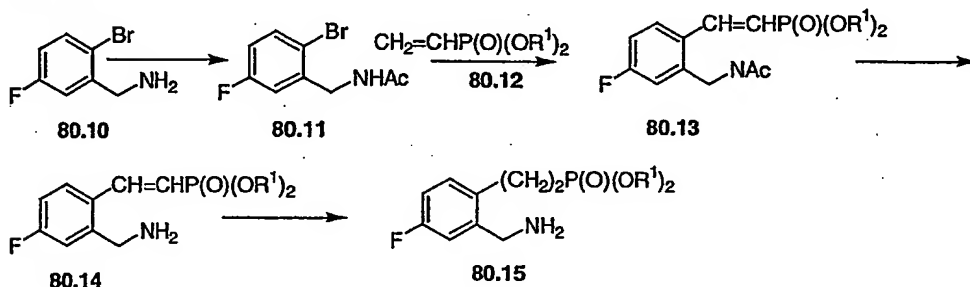


Scheme 80

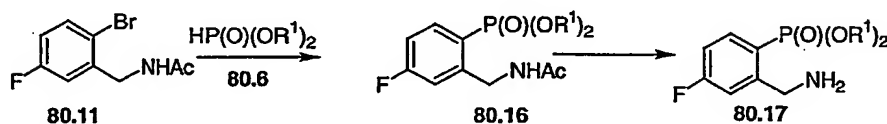
Method



Example 1



Example 2



Preparation of phosphonate-substituted fluorobenzylamines 39.4.

- 5 Schemes 81 and 82 illustrate the preparation of phosphonate-substituted 3-fluorobenzylamines 39.4 which are used in the preparation of the phosphonate esters 7.

Scheme 81 depicts the preparation of 3-fluorobenzylamines in which the phosphonate group is attached by means of an amide linkage. In this procedure, 3-fluorophenylalanine 81.1, (Alfa Aesar) is converted into the BOC derivative 81.2. The product is then coupled with a dialkyl aminoalkyl phosphonate 81.3 to afford the amide 81.4, which upon deprotection gives the amine 81.5.

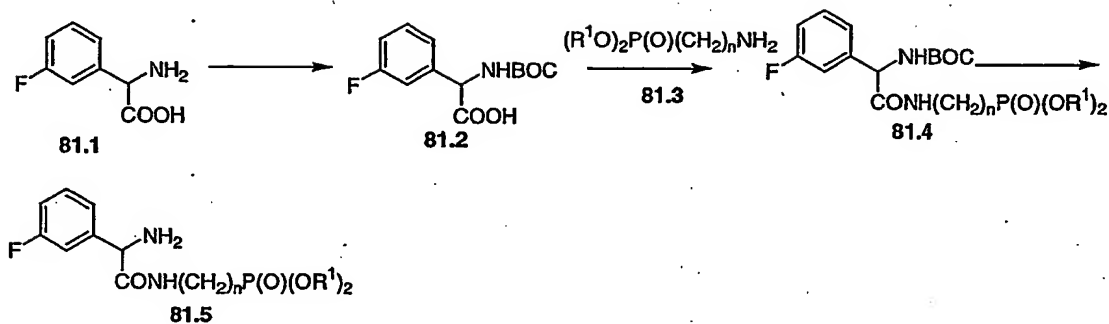
For example, the BOC-protected aminoacid 81.2 is coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminomethyl phosphonate 81.6 (Interchim), to prepare the amide 81.7. Deprotection then affords the amine 81.8.

Using the above procedures, but employing, in place of the amine 81.6 different amines 81.3, the corresponding products 81.5 are obtained.

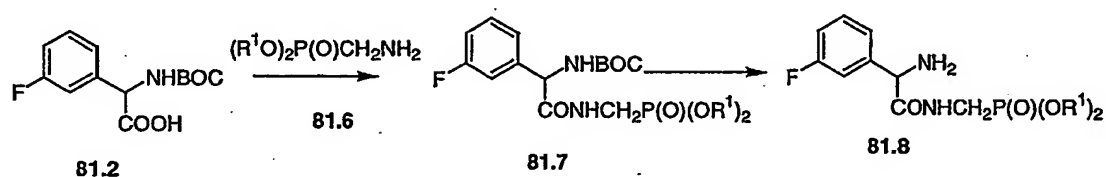
- Scheme 82 illustrates the preparation of fluorobenzylamine derivatives in which the
- 5 phosphonate group is attached by means of an alkyl or alkoxy chain. In this procedure, a hydroxyalkyl-substituted 3-fluorobenzylamine 82.1 is converted into the BOC derivative 82.2. This compound is then reacted with a dialkyl bromoalkyl phosphonate 82.3 to give the ether 82.4. The alkylation reaction is conducted in a polar organic solvent such as N-methylpyrrolidinone in the presence of a strong base such as sodium bis(trimethylsilyl)amide.
- 10 Deprotection of the product then affords the amine 82.5. Alternatively, the N-protected carbinol 82.2 is converted into the corresponding bromide 82.6, for example by reaction with N-bromoacetamide and triphenyl phosphine. The bromo compound is then reacted with a trialkyl phosphite in an Arbuzov reaction, as described above, to give the phosphonate 82.8, which upon deprotection affords the amine 82.9.
- 15 For example, 2-amino-2-(3-fluoro-phenyl)-ethanol 82.10, prepared as described in DE 4443892, is converted into the BOC derivative 82.11. The latter compound is then reacted in dimethylformamide at 100° with a dialkyl bromoethyl phosphonate 82.12 (Aldrich) and sodium hydride, to give the ether product 82.13. Removal of the BOC group then yields the amine 82.14.
- 20 Using the above procedures, but employing, in place of the carbinol 82.10 different carbinols 82.1, and/or different phosphonates 82.3 the corresponding products 82.5 are obtained. As a further example, the BOC-protected carbinol 82.11 is reacted with carbon tetrabromide and triphenylphosphine to produce the bromo compound 82.15. This material is heated at 120° with an excess of a trialkyl phosphite 82.7 to give the phosphonate 82.16. Deprotection then
- 25 yields the amine 82.17.
- Using the above procedures, but employing, in place of the carbinol 82.11 different carbinols 82.2, and/or different phosphonates 82.7 the corresponding products 82.9 are obtained.

Scheme 81

Method

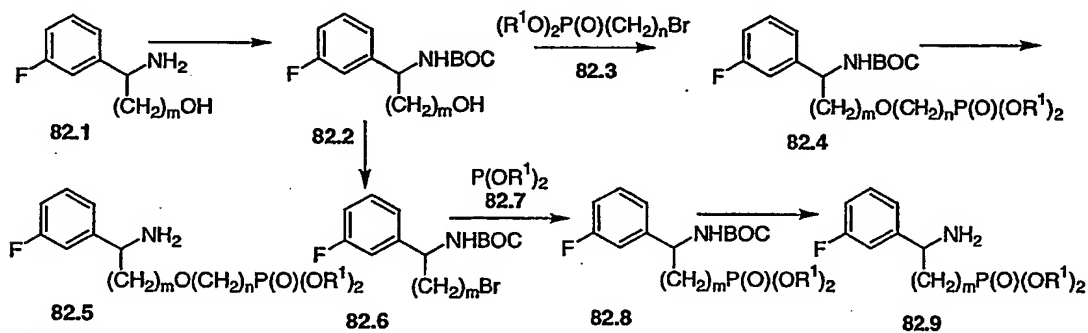


Example

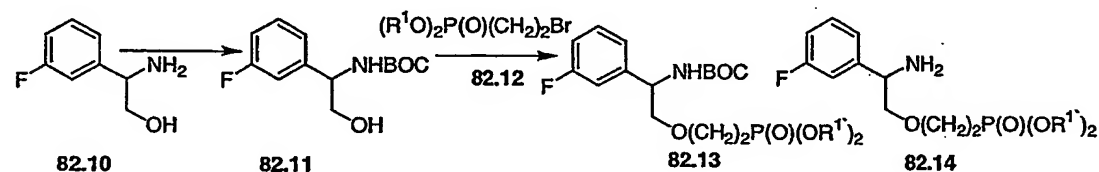


Scheme 82

Method



Example 1



5 Preparation of the phosphonate-containing tert. butanol derivatives 30.1.

Schemes 83 - 86 illustrate the preparation of the tert. butanol derivatives 30.1 which are employed in the preparation of the phosphonate esters 5.

Scheme 83 depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of an alkylene chain. In this procedure, a bromoalkyl carbinol 83.1 is reacted with a trialkyl phosphite 83.2 in an Arbuzov reaction, to afford the phosphonate 83.3.

5 For example, 4-bromo-2-methyl-butan-2-ol 83.4 prepared as described in Bioorg. Med. Chem. Lett., 2001, 9, 525, and a trialkyl phosphite 83.2 are heated at ca. 120° to produce the phosphonate 83.5.

Using the above procedures, but employing, in place of the bromo compound 83.4 different bromo compounds 83.1, and/or different phosphites 83.2 the corresponding products 83.3 are
10 obtained.

Scheme 84 depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of an amide linkage. In this procedure, a carboxylic acid 84.1 is coupled with a dialkyl aminoalkyl phosphonate 84.2 to afford the amide 84.3. The reaction is
15 conducted under the conditions previously described (Scheme 1) for the preparation of amides.

For example, equimolar amounts of 3-hydroxy-3-methyl-butyric acid 84.4, (Fluka) and a dialkyl aminoethyl phosphonate 84.5, the preparation of which is described in J. Org. Chem., 2000, 65, 676 are reacted in tetrahydrofuran in the presence of dicyclohexylcarbodiimide to
20 yield the amide 84.6.

Using the above procedures, but employing, in place of the carboxylic acid 84.4 different acids 84.1, and/or different amines 84.2 the corresponding products 84.3 are obtained.

Scheme 85 depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of a heteroatom and an alkylene chain. In this procedure, a hydroxy, mercapto or amino-substituted carbinol 85.1 is reacted with a dialkyl bromoalkyl phosphonate 85.2 to afford the ether, thioether or amine products 85.3. The reaction is conducted in a polar organic solvent in the presence of suitable base such as sodium hydride or cesium carbonate. For example, 4-mercapto-2-methyl-butan-2-ol 85.4 prepared as described in Bioorg. Med.
25 Chem. Lett., 1999, 9, 1715, is reacted in tetrahydrofuran containing cesium carbonate with a dialkyl bromobutyl phosphonate 85.5, the preparation of which is described in Synthesis, 1994, 9, 909, to yield the thioether 85.6.
30

Using the above procedures, but employing, in place of the thiol **85.4** different alcohols, thiol or amines **85.1**, and/or different bromides **85.2** the corresponding products **85.3** are obtained.

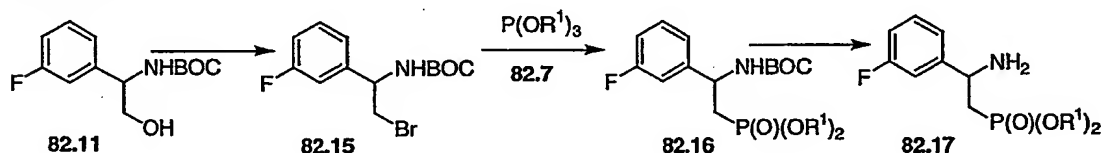
Scheme **86** depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of a nitrogen and an alkylene chain. In this procedure, a hydroxyaldehyde **86.1** is reacted with a dialkyl aminoalkyl phosphonate **86.2** under reductive amination conditions, as described above, (Scheme **55**) to afford the amine **86.3**.

For example, 3-hydroxy-3-methyl-butyraldehyde **86.4** and a dialkyl aminoethyl phosphonate **86.5** the preparation of which is described in J. Org. Chem., 2000, 65, 676 are reacted together in the presence of sodium triacetoxyborohydride, to yield the amine **86.6**.

Using the above procedures, but employing, in place of the aldehyde **86.4** different aldehydes **86.1**, and/or different amines **86.2** the corresponding products **86.3** are obtained.

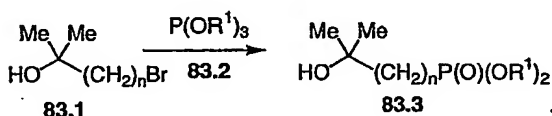
Scheme 82

Example 2

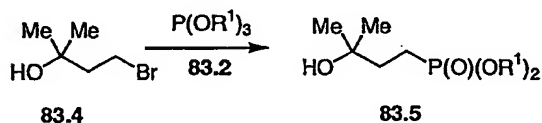


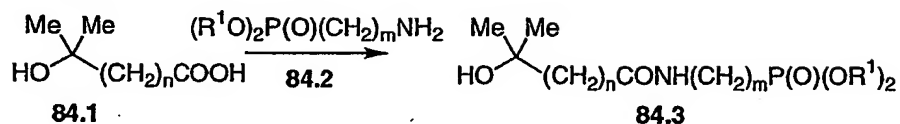
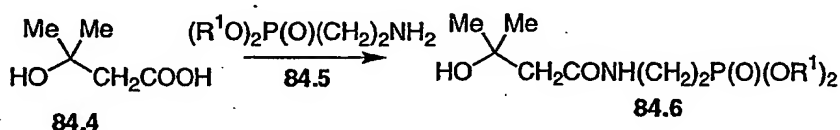
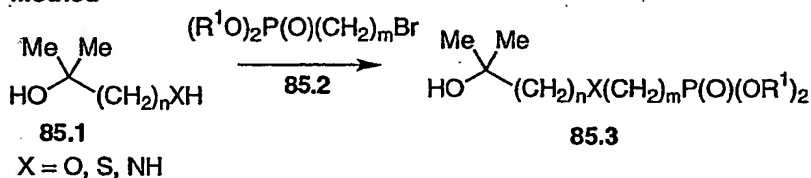
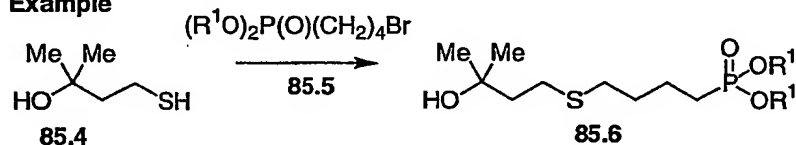
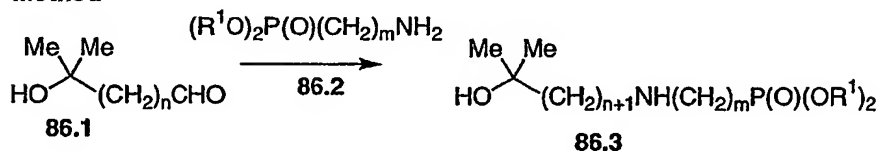
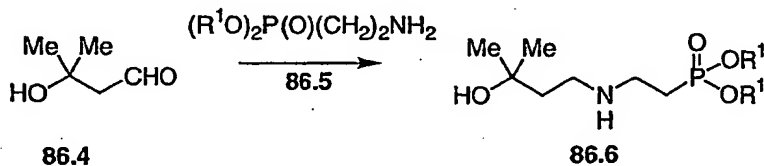
Scheme 83

Method



Example



Scheme 84**Method****Example****Scheme 85****Method****Example****Scheme 86****Method****Example****5 Preparation of the phosphonate-containing benzyl carbamates 43.4.**

Schemes 87 - 91 illustrate methods for the preparation of the benzyl carbamates 43.4 which are employed in the preparation of the phosphonate esters 9. The benzyl alcohols are obtained

by reduction of the corresponding benzaldehydes, the preparation of which is described in Schemes 87 - 90.

5 Scheme 87 illustrates the preparation of benzaldehyde phosphonates 87.3 in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde 87.1 is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate 87.2, under reductive amination conditions, as described above in Scheme 55, to yield the phosphonate product 87.3.

For example, benzene-1,3-dialdehyde 87.4 is reacted with a dialkyl aminopropyl phosphonate 10 87.5, (Acros) and sodium triacetoxyborohydride, to afford the product 87.6.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde 87.4, different benzene dialdehydes 87.1, and/or different phosphonates 87.2, the corresponding products 87.3 are obtained.

15 Scheme 88 illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated carbon chain. In this procedure, a bromobenzaldehyde 88.1 is coupled, as described above, with a dialkyl alkenylphosphonate 88.2, to afford the alkenyl phosphonate 88.3. Optionally, the product is reduced to afford the saturated phosphonate ester 88.4. Alternatively, the bromobenzaldehyde 20 is coupled, as described above, with a dialkyl phosphite 88.5 to afford the formylphenylphosphonate 88.6.

For example, as shown in Example 1, 3-bromobenzaldehyde 88.7 is coupled with a dialkyl propenylphosphonate 88.8 (Aldrich) to afford the propenyl product 88.9. Optionally, the product is reduced, for example by the use of diimide, to yield the propyl phosphonate 88.10.

25 Using the above procedures, but employing, in place of 3-bromobenzaldehyde 88.7, different bromobenzaldehydes 88.1, and/or different alkenyl phosphonates 88.2, the corresponding products 88.3 and 88.4 are obtained.

Alternatively, as shown in Example 2, 4-bromobenzaldehyde is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 88.5 to afford the 4-formylphenyl phosphonate 30 product 88.12.

Using the above procedures, but employing, in place of 4-bromobenzaldehyde 88.11, different bromobenzaldehydes 88.1, the corresponding products 88.6 are obtained.